



# NEW AND NONOFFICIAL REMEDIES, 1944

Containing Descriptions of the  
Articles Which Stand Accepted by the Council  
on Pharmacy and Chemistry of the  
American Medical Association  
on January 1, 1944

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Issued  
Under the Direction and Supervision of the Council on  
Pharmacy and Chemistry of the American  
Medical Association

AMERICAN MEDICAL ASSOCIATION  
535 NORTH DEARBORN STREET  
CHICAGO 10

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## PREFACE

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New and Nonofficial Remedies is a book in which are listed and described the articles that stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1 of the year of publication. The descriptions of accepted articles are based in part on investigations made by or under the direction of the Council and in part on evidence or information supplied by the manufacturer or his agents. Statements made by those commercially interested are examined critically and admitted only when they are supported by other evidence or when they conform to known facts.

While it is not the normal procedure of the Council to consider pharmacopoeial drugs such preparations have been included under special circumstances as explained in the Council's rules. A number of such articles are listed in the present volume. The Council recently decided to cease consideration of those official preparations the actions, uses and nature of which are so well understood by physicians as not to require their inclusion in New and Nonofficial Remedies. At the same time the Council took initial action to do away with the section known as List of Articles and Brands Accepted by the Council but not described in N. N. R. Many official articles no longer needing consideration were included in this section; others will be transferred to the main body of the book. Omission of this class of official articles has not yet been completed nor has the section referred to been entirely omitted; however some progress has been made in this direction and the articles so omitted are enumerated later in this preface.

In accordance with the Council's usual custom the general articles have been revised where necessary to bring them up to date. No radical revision of any chapter was found necessary; however more or less important revisions have been made in the following chapters: Barbituric Acid Derivatives, Nitrogenous Substances, Parathyroid, Ovaries, Sulfonamide Compounds, Vitamins, especially the sections Vitamin B Complex and Vitamin D. A noteworthy revision of the Vitamin chapter consists in the enumeration under the various vitamins of the limitations of potencies of the various preparations which the Council will consider for acceptance.

Solutions referred to in the descriptions of qualitative and quantitative tests are, unless otherwise stated, of the strength described. . . . . supplement  
in effect . . . . . Remedies  
Unless . . . . . in general  
refer . . . . .

The following articles which appeared in New and Nonofficial Remedies 1943 have been omitted either because of



the action referred to above or because they conflict otherwise with the rules that govern the recognition of articles or because convincing evidence to demonstrate their continued eligibility was not presented: Ampoule Solution Caffeine with Sodium Benzoate (Abbott); Ampoule Solution Caffeine with Sodium Benzoate (Endo); Ampoule Solution Caffeine with Sodium Benzoate (U. S. S. P.); Ampoule Sterile Solution Caffeine with Sodium Benzoate (Upjohn); Ampoule Solution Caffeine with Sodium Benzoate (Breon); Ampoule Solution Caffeine with Sodium Benzoate (Flint, Eaton); Ampoule Solution Caffeine with Sodium Benzoate-Lakeside; 0.24 Gm. in 2 cc. Solution Caffeine with Sodium Benzoate (Hyposols) (Products); Artificial Vichy Citrate (Dermo Co.); Benzoate (Upjohn); Lactopholus Milk Culture (Whole) (Whole) Milk (Supplee-Wills-Jones Milk Co.); Mercuropurin (Solution) (Campbell); Mercurin; Oxygen-Carbon Dioxide Mixture (Carbon Dioxide 5%, Oxygen 95%) (Denver Oxygen Co.); Oxygen-Carbon Dioxide Mixture (Carbon Dioxide 7%, Oxygen 93%) (Denver Oxygen Co.); Oxygen-Carbon Dioxide Mixture (Carbon Dioxide 10%, Oxygen 90%) (Denver Oxygen Co.); Oxygen-Carbon Dioxide Mixture: oxygen 90%, carbon dioxide 10% (Ohio Chemical & Mfg. Co.); Oxygen-Carbon Dioxide Mixture: oxygen 93%, carbon dioxide 7% (Ohio Chemical & Mfg. Co.); Oxygen-Carbon Dioxide Mixture: oxygen 95%, carbon dioxide 5% (Ohio Chemical & Mfg. Co.); "Pureco" Carbonic Acid Gas (Pure Carbonic) Riboflavin (Powder) .001 Gm. and 0.1 Gm. (Merck); Solution .5 cc. (Stearns); Solution .5 cc., 30 cc. vial (Breon); Tablets Cinchophen (Squibb); Tablets Neocinchophen (Squibb); Tablets Thiamine Theobromine

The statements concerning the actions, uses, or dosage of the following have been revised: Aminopyrine; Antidysenteric; Antidysenteric Serum;

Sulfate, benzene, Antitoxin; Brometol; Butylchloral Hydrate; Chlorobutanol; Chloroform Concentrate; Digitaline Native; Digitalol; Diodrast; Diodrast Compound

Solution, Irysipelas Streptococcus Antitoxin, Erythryl  
Tetranitrate Tablets, Lstrial (Thecelol), Estrogenic Sub  
stances Estrone, Lucatropine Hydrochloride, Evipal Sodium  
Gold Sodium Phiosulfate, Human Measles Immune Serum  
Human Scarlet Fever Immune Serum, Isotonic Solution of  
Sodium Chloride, Lunosc  
toxin Metaphen Neo S  
min A, Ouabain Pentou  
noston Sodium, Phenetsa  
Zinc Insulin, Quinidine  
(Pasteur)-(Pasteur Antir  
Alurate, Sodium Amy  
Staphylococcus Antitoxin  
Sulfapyridine Sodium  
Sodium, Sulfonamide Cc  
Acetate, Theophylline  
chloride, Urganin, Vioform, A U & D

The statem  
or strength c  
cases of the  
Allergenic E  
(U S S P),  
Anipoule Stei  
(Lederle), A  
Ampul Soluti  
Morrhuate 5% with Benzyl Alcohol (Searle) Ampules Ars  
phenamine (Merck), Ampules Benzedrine Sulfate Solution  
(Smith, Kline &  
Ampules Sterile  
Anesthesia (Squib  
tion (in oil) (  
Thiosulfate with  
Hydrochloride (Powder) (Novocain Chemical Mfg. Co.), Anti  
anthrax Serum (Lederle), Antimeningococcic Serum (Lederle),  
Barbital Sodium (Powder) (Merck), Benzedrine Benzedrine  
Inhaler (Smith Kline & French) Benzedrine Sulfate Benze  
drine Sulfate Tablets (Smith, Kline & French), Betabion  
(Powder) (Merck), Bismuth Ethylcamphorate Solution (In  
oil) (Upjohn), Capsules Concentrate of Vitamins A and D  
from C  
Corp)  
son); C  
(Powde  
Liver  
(White  
Liver  
Concentrate of Vitamins A and D from Cod Liver Oil in  
Vegetable Oil (International Vitamin Corp) Concentrated  
Pollen Antigen (Lederle), Dial (Powder) (Ciba), Digitaline  
Nativelle, Digitan, Diphtheria Toxin for Schick Test (In  
Peptone Solution) (National Drug), Eucatropine Hydro  
chloride (Powder) (Werner) Gas Gangrene Antitoxin Refined

and Concentrated (National Drug); Gelatin Compound Phenolized; Halibut Liver Oil (Mead Johnson); Haliver Oil Plain Capsules (Abbott); Ipral Calcium (Powder) (Squibb); Kelene (liquid) (Merck); Lunosol; Malt Extract with Cod Liver Oil (Borchardt Malt Extract Co.); Maltine with Cod Liver Oil (Maltine Co.); Measles Immune Serum (Human) (Milwaukee Convalescent Serum Center); Mecholyl Bromide (Powder) (Merck); Mercury Succinimide (Powder) (Merck); Mineral Oil (Squibb); Nicotinic Acid (Powder) (Merck); Normal Human Plasma (Citrated) bottle (Samuel Deutsch); Normal Human Plasma (Citrated) (Diluted) (Samuel Deutsch); Nupercaine Hydrochloride (Powder) (Ciba); Oleum Percomorphum 50% (Mead Johnson); Pentnucleotide; Phenazine Hydrochloride (Powder) (Werner Drug & Chemical Co.); Phenobarbital Sodium (Powder) (Gane & Ingram); Pollen Antigen (Lederle); Pollen Extract (Arlington); Pollen Extract (Cutter); Pollen Extract (Hollister-Stirr); Pollen Extract (Sharp & Dohme); Pollen Extract (Squibb); Proflavine (Powder) (National Aniline Div., Allied Chemical & Dye Corp); Protein Extract (Arlington); Pulvoids Thiamine Hydrochloride (Drug Products); Pyrethrum Ointment (Uphler Smith); Rabies Vaccine Human (Phenol Killed) (National Drug); Refined Diphteria Toxoid, Alum Precipitated (Lederle); Refined Diphteria Toxoid (Alum Precipitated) (National Drug); Refined Diphteria Toxoid, Alum Precipitated (Squibb); Scarlet Fever Immune Serum (Human) (Philadelphia Serum Exchange); Scarlet Fever Streptococcus Antitoxin, Refined and Concentrated (National Drug); Silver Pierate Crystals (Wyeth); Solhisminol Solution (Squibb); Sodium Amytal (Powder) (Lilly); Solargentum (Powder) (Squibb); Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil (International Vitamin); Soluble Gelatin Capsules Halibut Liver Oil with Viosterol (Squibb); Soluble Gelatin Capsules Haliver Oil with Viosterol (Abbott); Solution Colloidal Mercury Sulphide-Hille; Solution Liver Extract Parenteral, 2 U. S. P Units per Cc. (Parke, Davis); Solution Nikethamide 25% W/V (Breon); Staphylococcus Toxoid (National Drug); Sterile Solution Epinephrine Hydrochloride 1:1,000 (Lederle); Stovarsol (Powder) (Merck); Sulfanilamide (Powder) (National Drug); Sulfanilamide (Powder) (Squibb); Sulfathiazole (Powder) (Squibb); Tablets Ascorbic Acid (Squibb); Tablets Chiniofon, Hydrochloride (White Parke, Davis); Tablets Enteric C, Hydrochloride (White Parke, Davis); Tablets Urethane Antitoxin (National Drug); Tetanus-Gas Gangrene Antitoxin (Squibb); Tetanus Toxoid, Alum Precipitated, Refined (Sharp & Dohme); Tryparsamide (Powder) (Merck); Tuberculin B. E. (Concentrated) (Parke, Davis); Tuberculin Old and Control for the Pirquet Test (Parke, Davis); Tuberculin Old (Koch)

(Parke Davis), Unguentum Iurisci 10 per Cent (Hille)  
Urotropin (Powder) (Scherer & Glatz), Ventriculin (Parke  
Davis) Viosterol in Hydrot Liver Oil (Mead Johnson)  
Viosterol in Oil (McKesson & Robbins) Viosterol in Oil  
(Mead Johnson)

The following articles have been omitted as being off the market

Abbott &  
 Vaccine  
 (S & D  
 Ampoule  
 (Upjohn)  
 per cc  
 1 cc (Abbott)  
 (Abbott)  
 Bismuth  
 Toxin A  
 Solution  
 Solution  
 Corp) Ampul Solution  
 cc (Merrell), Ampul  
 mg per cc (Merrell)  
 chloride 10 mg per cc  
 Intravenous Injection  
 50% W/V 20 cc (B  
 & Westcott & Durr  
 (Merek) Ampul  
 Ampul Solution Nikethamide 25% W/V 5 cc Ampul  
 Solution Alcohol (Lakeside)  
 Antisepsis Serum  
 (Parke) Serum Concentrated  
 Type I (Squibb)  
 Type II (Squibb)

(Lederle) Antipneumococcal Serum (Rabbit)	Type 4	20 000
unt vial (Lederle) Antipneumococcal Serum (Rabbit)	Type	
5 20 000 unt vial (Le		
bit) Type 7 20 000		
Serum (Rabbit) Type		
pneumococcal Serum		
(Lederle) Antipneum		
trated Type I (Lederle)	Antipneumococcal Serum	Refine 1



cc (Upjohn), Mead's Mineral Oil with Malt Syrup (Mead Johnson) Mercurochrome Applicators (Arzol Chemical Co) Plague Vaccine, Prophylactic (Lilly), Pulvules Pentobarbital Sodium (Lilly), Rabies Vaccine (Cumming) (Parke Davis) Rabies Vaccine (Pasteur) (Gilliland) Refined Solution Liver Extract Parenteral 5 U S P Injectable Units per cc (Lederle), Saf T-Top Ampoules 5 per Cent Ferric Chloride in 50 per Cent Glycerin Solution (Bernhard), Saf T Top Isopropyl Alcohol, 98% (Bernhard), Saf T Top Mercurochrome 2 per Cent in 25 per Cent Glycerin (Bernhard) Saf T-Top Mercurochrome Solution 2 per Cent (Bernhard) Saf T-Top Tincture of Merthiolate 1 : 1000 (Bernhard) Saf T-Top Tincture Metaphen 1 : 200 (Bernhard), Scillaren (Powder) (Sandoz), Scillaren B (Powder) (Sandoz) Sodium Citrate 2½% W/V in Isotonic Solution of Sodium Chloride 35 cc 70 cc in 500 cc and 105 cc in 1000 cc Transfuso Vac containers (Baxter Labs), Sodium Citrate 2½% W/V in Isotonic Solution of Sodium Chloride 15 cc and 35 cc in Centri Vac containers of 300 cc (Baxter Labs), Sodium Citrate 2½% W/V in Isotonic Solution of Sodium Chloride 15 cc and 35 cc in Centri Vac containers of 300 cc (Don Baxter) Solution Epinephrine Hydrochloride 1 : 1000 (Lederle) Solution of Invert Sugar (Lilly) Solution Nicotinic Acid Amide (S M A) Solution Thiamine Hydrochloride 10 mg per cc (Merrell) Solution Thiamine Hydrochloride 50 mg per cc (Merrell) Staphylococcus Vaccine (Squibb), Sterile Dextrose 2½% W/V in Isotonic Solution of Sodium Chloride 2000 cc (Don Baxter) Sterile Dextrose 7½% W/V in Isotonic Solution of Sodium Chloride 500 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter) Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride 1000 cc and 2000 cc (Don Baxter)

Davis) Tetanus Antitoxin (Bovine) Refined and Concentrated (National Drug) Tetanus Antitoxin Globulin Modified (Lederle) Tuberculin B F (Bovine) (Parke Davis) Tuberculin Intracutaneous for Mantoux Test (National Drug) Typhoid Paratyphoid Mixed Vaccine 2.5 cc (Upjohn) Undulant Fever Vaccine (Abortus and Swis) 15 cc (National



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# OFFICIAL RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY

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## INTRODUCTION

**OBJECT OF THE RULES**—The following rules have been adopted by the Council primarily with the object of protecting the medical profession and the public against fraud, undesirable secrecy and objectionable advertising in connection with proprietary medicinal articles.

Today the purpose of the Council is still to protect the public and the medical profession against deception and objectionable advertising of proprietary medicinal articles, but it is also the function of the Council to advise the medical profession concerning the status of medicinal articles it is importuned to use to publish reports on claimed advances in the use of drugs and to elaborate standards for the control and identity of drugs that are introduced into materia medica.

**Contents of A. N. R.**—The book *New and Nonofficial Remedies* contains a description of proprietary articles which have been accepted as conforming to the rules of the Council of such simple nonproprietary and nonofficial substances as seem of sufficient importance to warrant their inclusion and of simple pharmaceutical preparations the inclusion of which is believed to give useful information to physicians.

*Attitude on Medicament mixtures & compliance they ever, endorses the basis of the therapeutic reason it includes real advantage.*

## RULES GOVERNING THE ADMISSION OF PROPRIETARY ARTICLES TO THE BOOK NEW AND NONOFFICIAL REMEDIES

**DEFINITION OF PROPRIETARY ARTICLES**—The term 'proprietary article' in this place shall mean any chemical, drug or similar preparation used in the treatment of diseases if such article is protected against free competition as to name, product, composition or process of manufacture, by secrecy, patent or copyright, or by any other means.

**Rule 1**—**COMPOSITION**—No article will be accepted for inclusion in the book *New and Nonofficial Remedies* or retained therein unless its composition is published. For simple substances the scientific name and the chemical formula, rational or structural if known should be supplied. For mixtures, the amount of each active medicinal ingredient in a given quantity of the article must be stated. The general composition of the vehicle, its alcoholic percentage and the identity of the preservatives must be furnished.

**Rule 2**—**IDENTIFICATION**—No article will be accepted or retained unless suitable tests for determining its composition

are furnished to the Council. In the case of chemical compounds, these shall consist of tests for identity and purity. In the case of mixtures, description of methods for determining the amount and strength of the potent ingredients shall be furnished, if practicable.

*Rule 3.—DIRECT ADVERTISING.*—No article that is advertised to the public will be accepted or retained; but this rule shall

intestinal and genitourinary tracts) and provided they are not advertised as curative agents (see comments to Rule 3); (b) liquid petrolatum and simple preparations of liquid petrolatum, agar and simple preparations of agar, and similar preparations which act because of their bulk, provided that such lay advertising carries a warning that agar and similar preparations may be harmful in colitis; (c) other agents about which the public should be informed and which would not lead to harmful self-medication provided (1) that they are not advertised as curative agents and provided (2) that the advertising to the public does not go beyond that passed by the Council for physicians (Rule 6).

*Rule 4.—INDIRECT ADVERTISING.*—No article will be accepted or retained if the label, package or circular accompanying the package contains the names of diseases in the treatment of which the article is said to be indicated. The therapeutic indications and properties may be stated, provided such statements do not suggest self-medication. Dosage may be indicated. (This rule shall not apply to remedies with which self-medication is altogether improbable, to vaccines and antitoxins, or to directions for administering or applying remedies when similar immediate, heroic treatment is indicated.)

*Rule 5.—FALSE CLAIMS AS TO ORIGIN.*—No article will be accepted or retained concerning which the manufacturer or his agents make false or misleading statements as to source, raw material from which made or method of collection or preparation.

*Rule 6.—UNWARRANTED THERAPEUTIC CLAIMS.*—No article will be accepted or retained concerning which the manufacturer or his agents make unwarranted, exaggerated or misleading statements as to the therapeutic value.

*Rule 7.—POISONOUS SUBSTANCES.*—The principal label on an article containing "poisonous" or "potent" substances must state plainly the amount of each of such ingredients in a given quantity of the product.

*Rule 8.—OBJECTIONABLE NAMES.*—Proprietary names for medicinal articles will be recognized only when the Council shall deem the use of such exclusive names to be in the interest

of public welfare. Names which are misleading or which suggest diseases, pathologic conditions or therapeutic indications will not be recognized (the provision against therapeutically suggestive names does not apply to serums, vaccines and anti-toxins). In the case of pharmaceutical preparations or mixtures the name must be so framed as to indicate clearly the most potent ingredients. Coined names for salts will not be accepted unless such names indicate the components of the salt, coined names for new substances marketed as pharmaceutical preparations will not be accepted unless such names indicate definitely the type or dosage form of the article.

**Rule 9 — PATENTED PRODUCTS AND PROTECTED NAMES** — If the article is patented—either process or product or both—the number of such patent or patents must be furnished to the Council. Furthermore if the name of an article is registered or the label copyrighted the registration (trademark) number and a copy of the protected label should be furnished the Council. In case of registration in foreign countries the name under which the article is registered should be supplied.

**Rule 10 — UNSCIENTIFIC AND USELESS ARTICLES** — No article will be accepted or retained which because of its unscientific composition is useless or inimical to the best interests of the public or of the medical profession.

**Rule 11 — POLICIES OF FIRMS DETRIMENTAL TO RATIONAL THERAPEUTICS** — The Council will not accept or retain if already accepted the articles of a firm if in the opinion of the Council the policies of such a firm are clearly detrimental to the welfare of the public and to medicine.

#### EXPLANATORY COMMENTS ON THE RULES

**PURPOSE AND METHODS OF THE COUNCIL** — The Council on Pharmacy and Chemistry was established in 1905 by the American Medical Association primarily for the purpose of gathering and disseminating such information as will protect the medical profession in the prescribing of proprietary medicinal articles. In pursuance of this object the Council examines the articles on the market as to their compliance with definite rules designed to prevent fraud, undesirable secrecy and the abuses which arise from advertising directly or indirectly to the laity. Such articles as appear to conform to the rules are accepted and their essential features are described in the annual publication of the Council, *New and Nonofficial Remedies*, if they come within the scope of this book.

**Submitted Evidence** — These descriptions are based in part on investigations made by or under the direction of the Council but in part also on evidence or information supplied by the  
 "sted statements are  
 if they appear to be  
 however, manifestly  
 the composition of  
 every complex pharmaceutical mixture or to check thoroughly

every therapeutic claim; it can give only unbiased judgment on the available evidence. Criticisms and corrections of the descriptions which may aid in the revision of the matter will be appreciated.

*Previous Noncompliance and Fraud.*—The Council judges an article entirely by the facts in evidence at the time of its admission. Previous noncompliance with the rules (short of intentional fraud) does not prevent the favorable consideration of an article which is in accord with existing rules.

of . . . . . rules after acceptance  
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*Acceptance Not an Indorsement.*—The Council desires physicians to understand that the admission of an article does not imply a recommendation. Acceptance simply means that no conflict with the rules has been found by the Council.

*Seal of Acceptance*—For articles which are accepted for inclusion in New and Nonofficial Remedies or in the List of Articles and Brands Accepted by the Council but Not Described in N. N. R., the Council permits the use of its official seal of acceptance, with the following stipulations: (1) The seal may be used on the packages of an article and in the advertising for it. (2) The seal, if used, must be the only seal of such character to appear. No objection is made, however, to any statement or device required or permitted by the government indicating compliance with regulations of a government bureau or department. (3) If the seal is used in price lists and catalogs which also feature unaccepted articles, it must be used for accepted articles in such a manner that there can be no implication that the seal applies to the unaccepted articles. (4) The following statement in reference to the significance of the seal may be used in connection with the seal: "The 'accepted' seal denotes that [name of article] has been accepted for New and Nonofficial Remedies by the Council on Pharmacy and Chemistry of the American Medical Association." Further statements in regard to the seal must be submitted to the Council and found acceptable before they may be used. (5) The size of the seal on the package shall not be greater than one inch in height or diameter, and in advertising it shall be in proportion to the dimensions of the advertisement so as to afford ready recognition; but undue size, giving greater prominence to the seal than to other important features of the advertisement or detracting from the dignity of the seal in the opinion of the Council, will not be permitted. (6) When for any reason the acceptance of an article is rescinded, the seal must not appear on new labels or in new advertising for such

article, and old labels and advertising which feature the seal must not be in circulation, in evidence, or before the public longer than six months subsequent to notification of the revocation

*Duration of Acceptance*—Unless otherwise determined at the time of acceptance, articles admitted to New and Nonofficial Remedies will be retained for a period of three years provided that during that period they comply with the rules and regulations which were in force at the time of their acceptance. New evidence indicating that compliance with the rules no longer exists for instance, with regard to unwarranted therapeutic claims will be considered the basis for reconsidering the acceptance before the end of a period of three years. At the end of this period all articles will be carefully reexamined for compliance with existing rules. Particular weight will be given to the question as to whether recent evidence has substantiated claims as to the therapeutic value of any preparation, this evidence to consist partly of recent statements in the literature and partly of the general esteem in which the preparation is held by clinical consultants of the Council. The reacceptance of articles after such reexamination shall be for three years unless a shorter period is specified.

Any amendments to the rules by specific requirements or by interpretation which may be made after the acceptance of an article shall not apply to such article until the period of acceptance has elapsed. At the end of this period the article if it is not eligible under the amended rules, will be omitted.

*The Scope of New and Nonofficial Remedies*—To aid physicians and manufacturers in deciding which articles come within the scope of this book, or, in other words, to enable

ing more detailed definitions

*Official Articles*—Articles official in the U S P or N F are exempted from consideration by the Council if they are marketed under the official name or a name which makes their official status evident and if no unestablished therapeutic claims are made for them.

These do not require consideration by the Council since standards for them are provided in these books, and enforced under the provisions of the Federal Food, Drug and Cosmetic Act except that they may be mentioned for information.

If a U S P or N F product is offered for sale under a name which does not make its official status evident or if the proprietors or their agents advance claims that the product possesses therapeutic properties other than those properly and commonly accredited to it it becomes subject to consideration by the Council.



Simple preparations or mixtures of official articles may be considered to have the status of official articles if they are marketed under descriptive, nonproprietary names and if unestablished claims are not made for them. At the request of the distributors of such products the Council will determine whether they meet these provisions, and if they are found not to require inclusion in N. N. R. they will be included in a list of articles and brands accepted by the Council but not described in N. N. R.

*Modifications of U. S. P. and N. F. Products.*—A Pharmacopeial or National Formulary product which is marketed under the official title or synonym, but with well-founded claims that its purity, permanence, palatability or other physical properties excel the official standard, may, if no extraordinary therapeutic properties are asserted, be considered as an official article and held not to be within the scope of New and Non-official Remedies.

When such products are marketed under the claim that they possess therapeutic properties other than those commonly accredited to the U. S. P. or N. F. products of which they are modifications, they become subject to the consideration of the Council.

The burden of proof in establishing claims for therapeutic properties of products considered by the Council shall lie with the proprietor or, in the case of a foreign-made product, with the agent who markets the product in the United States.

*Substances Described in New and Nonofficial Remedies.*—In the book will be described simple proprietary substances and their preparations; proprietary mixtures if they have originality or other important qualities which, in the judgment of the Council, entitle them to such place; important nonproprietary nonofficial articles; simple pharmaceutical preparations; or any other article, the inclusion of which is believed to give useful information to the physician. An article will not be accepted or retained unless it is found in the open market under the name of the firm under which it is submitted or accepted. The term "open market" contemplates both the wholesale and retail merchandizing drugs.

*Proprietary Mixtures*—A mixture will be considered as proprietary, and therefore requiring consideration by the Council for admission to the book, if it contains any proprietary articles, if it is marketed under a name which is in any way protected or if its manufacturer claims for it any unusual therapeutic qualities.

*Diagnostic Reagents*—Reagents and other drug preparations which are not used in or on the human body, and protein preparations used for diagnosis only shall not be considered for inclusion in N. N. R. At the request of the distributor

the Council will determine the status of such products individually, and if the product is found not to require inclusion in N N R it will be included in a list of Articles and Brands Accepted by the Council not Not Described in N N R.

*Suffix N N R*—When nonproprietary articles included in New and Nonofficial Remedies are prescribed, the Council recommends that they be indicated by the abbreviation 'N N R,' thus insuring to the prescriber the quality of these articles laid down in the book.

*Rule 1—Composition—Secrecy Objectionable*—It is not only the right but also the duty of the physician to know the essential composition of what he prescribes, the Council cannot compromise on this proposition.

*Statement of Composition*—In the case of a definite chemical substance, a descriptive name, satisfactory to the Council must appear on the label and in the advertising. For mixtures the label and advertising must contain a statement of the amount of each potent or important ingredient in a given quantity of the mixture. In the case of solutions marketed in the form of ampules the term 'cc size' will be accepted as a proper indication of the volume of contents the significance of the term being understood to be that the ampule contains a sufficient excess of the medicament to permit the withdrawal and administration of the dosage indicated by the size denomination. Individual ampules, or unit packages thereof must bear a statement explaining the significance of the term "cc size" as it applies in a given instance. For example if ampules are labeled "2 cc size" a satisfactory statement will be "Each ampule contains a sufficient amount (or excess) to permit withdrawal and administration of 2 cc."

*Vehicles and Preservatives*—In the case of mixtures, not only the potent ingredient, but also the general character of the vehicle the presence of alcohol and the identity of preservatives, or of any other substance, whether added or present as an impurity, must be stated if these can under any circumstances affect the therapeutic action of the article. Thus as a rule, does not mean the publication of trade secrets, such as flavors or the details of the working formula.

In the case of preparations for parenteral injection the identity and amount of preservatives must be declared in the labeling preferably on the individual container label but, where that is impracticable, on the carton label or individual package insert, in the event that no preservative is present, the absence must be declared. The definition of 'preservative' is intended to include all substances used for the purpose of preserving the identity, strength quality or purity of a preparation. Thus not only bactericidal or bacteriostatic agents are required to be declared in the labeling but other chemicals such as stabilizers, antioxidants and buffers.

*Trade Secrets*—Furthermore, trade secrets will not be received as confidential by the Council, since it accepts information only with the distinct understanding that this may be freely published, at its discretion.

*Inspection of Factories*.—The Council does not accept invitations to inspect factories; its concern is with the finished products.

On the other hand, the Council requires that the information be complete and accurate as to medicinal ingredients.

*Nonofficial Constituents*.—Nonofficial constituents of proprietary mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted.

*Fraud*—When it appears that a manufacturer has made a *deliberately* false statement concerning a product, he is asked to furnish an explanation; and if this is not satisfactory, the product will not be accepted, even if the false statement is subsequently corrected or omitted.

*Testimonials*.—The foregoing paragraph applies not only to statements made to the Council, but also to statements furnished to physicians by the manufacturer or his agents, even when these statements are in the guise of testimonials.

*Rule 2—IDENTIFICATION*.—In order to avoid errors in the case of chemical compounds, and to guard against adulterations, lack of potency or strength and the mistaking of one chemical for another, it is necessary to have at hand suitable tests.

*Tests, etc.*—If these facts have appeared in the literature, or in standard textbooks, reference to them will be sufficient; but with new chemicals, especially synthetics, the manufacturer or his representatives will be required to supply such tests for publication as will assure an intelligent opinion of these products.

*Physiologic Standardization*.—In cases in which chemical methods of identification are unknown or unreliable, physiologic standardization should be employed. The Council considers the phrase "physiologically standardized" or "assayed" as misleading unless the standard and method are published in sufficient detail to permit of their control by independent investigators.

It is evident that when no standard is published, it is impossible to know whether the quality is high or low, and the conscientious manufacturer who sets for himself a high standard is placed on a level with the dishonest or careless one who adopts a low standard. Again, if the process of standardization is not published, it is impossible to learn, without actual trial, the relative value of one preparation as compared with that of another manufacturer or to confirm or disprove the statement of the manufacturer as to the quality of his product.

*Standardization of Disinfectants and Germicides*—No disinfectant or germicide of the phenol type will be accepted for inclusion in New and Nonofficial Remedies whose phenol coefficient determined by the U S Food and Drug Administration method of testing antiseptics and disinfectants as given in Circular No 198 U S Dept of Agriculture is not stated on the label of the preparation

*Rule 3 — DIRECT ADVERTISING — Lay Advertising* — The impossibility of controlling the irresponsible claims which are usually made in advertisements to the public, the well known dangers of suggesting by descriptions of symptoms to the minds of the people that they are suffering from the many diseases described the dangers of the unconscious and innocent formation of a drug habit, and the evils of harmful self medication including the dangers of the spread of many infectious and contagious diseases when hidden from the physician, and similar well known considerations, are the reasons for discouraging in the interest and for the safety, of the public this reprehensible form of exploitation. Advertising in medical journals, and other publications distributed solely to physicians or in journals for dentists pharmacists nurses and veterinarians, does not come within the scope of this rule provided such advertising does not invite or encourage use by unqualified persons

*Exceptions*—In the case of subjects on which the public should be instructed as in the use of certain disinfectants germicides antiseptics laxatives and such other articles as the Council may specify, advertisements to the public if not in objectionable forms are considered admissible. In no case shall such advertisements include recommendations for use as curative agents nor shall the names of any diseases appear on or in the trade package except in connection with prophylactic recommendations. If the preparation is sufficiently toxic to require caution in its use to prevent poisoning this fact shall be stated on the label. On account of the deplorable results which would follow any abuse of this privilege the conscientious cooperation of manufacturers and their agents in adhering strictly to the limitations laid down is asked and for the same reason the acceptance of an article which is so advertised as to infringe on these limitations in any essential way (as by naming diseases or by making false and exagger

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Enforcement of the rule will be followed by deletion of the article and by publication of the facts as described

*Advertisements in Foreign Countries* — The Council deals primarily in the interests of the public and of the medical

profession, with articles proposed for admission to New and Nonofficial Remedies, and, in determining the status of any article, must take into consideration any statements made regarding it or any method of advertising it employed by the manufacturer or his authorized agents or representatives, whether in this country or abroad. The Council will not regard as within its scope, however, questions concerning the marketing of articles (except the matter of direct advertising to the laity and unwarranted claims or misrepresentations) outside the United States.

**Rule 4—INDIRECT ADVERTISING.**—It should be remembered that the sole intent of this rule is to protect the physician, so that in prescribing a proprietary medicine he shall not unconsciously advertise proprietary preparations. The rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession, such as advertising in medical journals, circulars and other printed matter distributed solely to physicians. The rule applies only to the package as it may reach the patient.

**Naming Diseases on Label.**—The naming of diseases on the label or package is not necessary, as is shown by the very large number of proprietary products which have been successfully introduced without resorting to this expedient. This method of popularizing a proprietary remedy with the laity is most objectionable, and should not be tolerated in any form.

**Therapeutic Indications.**—In general, therapeutic indications should be omitted from the label and package. The Council will not insist on this point, however, when such indications are so given as not to promote self-medication, particularly in diseases which require expert diagnosis and supervision.

**Permanently Affixed Names.**—It will be considered an infringement of the rule if an article is marketed in bottles which have the name of the article blown into the glass, or if otherwise the name or initial or other distinctive mark of the article is permanently stamped on the container, on the article itself, or is on the stoppers or seals. Articles which are marketed in any of these ways are not accepted for New and Nonofficial Remedies. Ready removable labels are not objectionable nor is the permanent affixing of the firm's initials or name to the trade package if such initials or name is not suggestive of the article.

**Use of Articles for Advertising.**—The Council does not countenance the use of an accepted article for advertising other articles which have not been accepted by the Council. The Council therefore objects to the mailing of circulars for accepted and unaccepted articles in one envelop if misleading statements are made in regard to the status of the various preparations under the Council's rules; if there is reason to believe that the method of presentation will tend to mislead the reader; and if it is not made clear beyond doubt which of the products have

been accepted by the Council, and which have not been accepted. This clause does not apply to advertising material circulated exclusively to dealers. The Council takes no exception to the use of the abbreviation "N N R" as a means of distinguishing Council accepted articles in those instances where the grouping of accepted and unaccepted products together is deemed likely to be misleading or confusing from the standpoint of their Council status. Nor will the Council accept an article or continue the acceptance of an article if the same article or an essentially similar one is marketed by the same firm under another name which has not been recognized. When, in the opinion of the Council, a firm secures the acceptance of one or more articles and employs the acceptance in a way that promotes the exploitation of articles that are opposed to the principles of the rules of the Council, the preparations of the firm will be dismissed summarily and no preparations of that firm will be accepted by the Council.

**Rule 5—FALSE CLAIMS AS TO ORIGIN**—No false or misleading statement in regard to an article can be permitted concerning the source or material from which it is made, or the persons by whom it is made. Some glaring frauds of this nature have been perpetrated in the past, and this rule is intended to prevent such imposition.

**Rule 6—UNWARRANTED THERAPEUTIC CLAIMS**—This rule insists that the claims of manufacturers or agents concerning the therapeutic properties of their products must be compatible with demonstrable facts. Manufacturers will be held responsible for all statements made or quoted in their advertising "literature" regarding their products. The use of the personal signature of a physician, or the facsimile of such signature on the label, or in advertising of products is objectionable because it tends to create, through the implication of personal supervision, an exaggerated or misleading impression of therapeutic value, and articles so labeled or advertised are therefore not acceptable. Therapeutic claims made subsequent to the acceptance of an article must be submitted to the Council for review, provided such claims exceed or substantially modify those made at the time of acceptance. Recognizing the existence of honest differences of opinion on many therapeutic questions the Council desires to be liberal in the application of this rule. It is natural that a manufacturer should be partial toward his own product, and a moderate degree of emphasis in advertising may not be objectionable. The Council however, will not admit claims which are neither in harmony with already accepted facts nor supported by acceptable evidence. In passing on advertising material the Council endeavors to indicate the type of claims which are acceptable and the nature of objectionable statements. It is not a function of the Council to edit advertising copy word for word and sentence for sentence,

but rather to indicate the general type of revision required in any given piece of advertising copy. The Council holds the firm responsible for compliance with the specifications of the Council's objections and expects the spirit and intent of such objections to be observed in the remainder of the copy not specifically criticized. Advertising copy which has been accepted by the Council may be used in whole or in part in later advertising, provided that this does not exceed the scope, content and purpose of the original material, and provided that there have not been any developments which would invalidate the original material. In doubtful cases the Council considers these questions with the advice and cooperation of its staff of clinical consultants.

Therapeutic claims that do not exceed the statements in the current New and Nonofficial Remedies will not be challenged as a rule; but if the Council finds reason to doubt the validity of any description in New and Nonofficial Remedies, it may require the manufacturer to submit further evidence if he desires to continue such claims. Since the claims of the manufacturers are judged largely by their advertising, noncompliance of the manufacturers with the Council's request for copies of the current advertising may be sufficient ground for the rejection of an article, unless in individual cases the Council deems such submission unnecessary. The Council holds that the terms "advertising" and "advertising literature" include films and similar devices for informing the public or the profession.

*Clinical Evidence.*—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions drawn. The amount and character of the evidence which is required depends on the inherent probability of the claims: No evidence is needed for a self-evident claim; very strong evidence is needed when the claim is contrary to the accepted data of science. The acceptability of evidence is determined mainly by its quality. The mere multiplication of inaccurate observations does not render them accurate. The evidence must be furnished in sufficient detail to permit judgment as to the care with which it was gathered and the legitimacy of the deductions. Comparative trials facilitate and are often necessary for such judgment. Observations that are not described with sufficient detail to permit verification are subject to suspicion. The credibility of the data and the justification of the deductions is influenced by the reputation and experience of the investigators, as to disinterestedness, technical ability and critical sense. Anonymous communications and observations gathered without adequate facilities are usually worthless as evidence.

*References to Medical Literature.*—References to medical literature in advertising for an accepted product should be

accompanied by the name of the investigator and the year of publication, or by full reference to the publication to which reference is made

**Rule 7—POISONOUS SUBSTANCES**—For the information of the pharmacist or dispenser, and to enable him to safeguard the interests of the patient and the physician, all articles containing such potent agents as the poisonous alkaloids and other organic substances and the salts of some of the metals should have the exact amount of these ingredients which is contained in the average adult dose stated on the label

**NOTE**—The Council wishes it understood that any claims of nontoxicity that are made for drugs that have or are supposed to have important general effects are admitted to this book only when they do not conflict with known facts. In all such instances however, it is recommended that a claim of lack of toxicity be not accepted too freely, but be considered to mean only that toxic effects have not as yet been recognized with the doses that have been studied. The most sincere and apparently justified beliefs concerning this point are often ultimately reversed by extended experience. Much the same may be said regarding any claims that drugs are nonirritating

**Rule 8—OBJECTIONABLE NAMES**—Many of the abuses connected with proprietary medicines arise from "coined" proprietary trade names. Such names will not be recognized by the Council unless in particular instances the Council shall deem their use to be in the interest of public welfare. In every such exception the burden of proof both for establishing and for continuing the exception, lies with those who market the product

**Proprietary ( Trade ) Names, When Permitted**—In consideration of the benefits which may come from the discovery of a therapeutic agent the Council concedes to the person or firm which by right of discovery, controls such a product the right to name it. The Council will offer no opposition to an arbitrary name for such a new product, provided it is not misleading therapeutically suggestive or otherwise subversive of scientific pharmacy and therapeutics. If the discovery that a previously known substance has therapeutic value is deemed of sufficient importance, the Council may recognize a name for such a substance if the name is applied by the person who makes the discovery, or, with the consent of the discoverer or in the absence of any protest on his part the Council may recognize a name applied by the firm which first makes such a product available to physicians. Under these conditions the Council may also recognize proprietary names when new uses or actions of exceptional novelty and importance are discovered for substances previously used in medicine, but which had become practically obsolete. In the interest of rational drug therapy the Council recommends that trade names be coined



so as to indicate the potent element or constituent. Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases in which the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising, unless the numeral or letter is clearly separated from and subordinated to the name by type, and if feasible by position. This rule shall not apply to price lists and catalogs.

When the proprietary or trade name for an article is considered insufficiently descriptive of its chemical composition or pharmaceutical character, the Council may require as a condition for the acceptance of such articles that a descriptive scientific name satisfactory to the Council appear on the labels, circulars and advertisements for such an article. For all definite chemical substances it is required that the scientific (chemical) name be given prominence on the labels, in circulars and in advertisements; provided that for those substances for which there are recognized Council or pharmacopeial names, such names shall be used and the scientific (chemical) name need not appear.

*Proprietary Names for Unoriginal Articles* — Proprietary names will not be recognized for articles which are included in the U. S. Pharmacopeia or National Formulary or for articles which are already accepted in New and Nonofficial Remedies or for unessential modifications of such articles. Neither will proprietary names be recognized for substances or mixtures which are described in medical or pharmaceutical publications, except in connection with fundamentally important discoveries relating to articles the use of which had become practically obsolete.

In the marketing of unoriginal articles, the legitimate interests of the producer are fully served by identifying such products by appending the name or initials of the manufacturer or agent, or by the use of a general brand mark. No objection will be made by the Council to the use of such brand marks, provided that in no case shall such mark be used as a designation for an individual article. Names, initials or brand marks of manufacturers or agents when used to denote proprietorship shall not be of such character as to cause any misunderstanding or confusion as to their significance.

For any product which, by reason of the absence or lapse of patent rights or for other reasons, is open to manufacture by more than one firm, the Council reserves the right to select

a common name and to provide standards of identity, purity and strength. The Council then will accept such article only if it is marketed under the title adopted as the N N R name or the name under which such article was introduced (to which may be appended the firm's identifying mark).

When an article which has been accepted for New and Non official Remedies is admitted to the U S Pharmacopeia or National Formulary, it will be omitted from New and Non official Remedies one year after such standardization if the name of such article is used in these standards either as the main title for the product or as a synonym. If the name under which the article is described in New and Nonofficial Remedies is not used in these books of standards the proprietary preparation will be retained provided the official name is given prominence on the labels and in the circulars and advertisements of such article.

When the Council adopts a common name for an article that has been admitted under another name, it will be continued under the older name only on condition that the Council name be given prominence on the label and in the circulars and advertisements for such article.

*Pharmaceutic Preparations and Mixtures*—These, with rare exceptions, are not original in composition and should not be endowed with uninforming names. It is important that they be so named as to remind the prescriber constantly of their potent ingredients. When in the rare exception a pharmaceutic preparation or mixture is accepted with a coined name on the ground of originality because it presents a distinct improvement over available preparations only the first preparation of this kind which is placed on the market shall be recognized under a coined name (which however, must clearly indicate the potent constituent of the preparation). The Council may also recognize coined names for pharmaceutic preparations or mixtures that were in actual use before the establishment of the Council and that have been used continuously since that time and names for mixtures that were named under the reasonably justified bona fide belief that they were chemical compounds provided that such coined names indicate the potent ingredient or ingredients of the preparation are not misleading and do not suggest diseases, pathologic conditions or therapeutic indications.

Difficulty frequently arises from the application of coined names to salts. For example a firm introduces the hydrochloride of a synthetic base under the name "Artificialin". Subsequently the firm decides to introduce the lactate of the same base. If this is called "Artificialin lactate" the name "Artificialin" will now mean the base instead of the hydrochloride which is being marketed under that name. In order to avoid this confusion the Council holds that coined names

for salts will not be accepted unless such names indicate the components of such salts, thus "Artificialin hydrochloride"; the name "Artificialin," unqualified, is acceptable only for the base. A similar difficulty may arise when a product is marketed first only as a pharmaceutical preparation to which the manufacturer wishes to apply a short coined name, for example, an elixir of a new hypnotic under the name "Aliphal." If later, the manufacturer elects to market the substance also in powder form, an entirely new name would become necessary and this would cause confusion both to the profession and to the trade. The Council therefore holds that coined names for new substances marketed as pharmaceutical preparations will not be accepted unless such names indicate the type or dosage form of the preparation; thus "Elixir of Aliphal," "Aliphal Powder," not "Aliphal" unqualified.

**Biologicals.**—A biological product intended for use as diagnostic reagent, vaccine, or as an antibacterial or antitoxic serum, should be designated by a name which indicates its biological nature (e. g. tuberculin, rabies vaccine, diphtheria toxoid, anti-pneumococcic serum, tetanus-gas gangrene antitoxin, or diphtheria antitoxin, globulin modified), and not by a coined name.

**Contraceptive Preparations.**—These preparations are not therapeutic agents and the physician is not especially interested in their ingredients but only in the sum total of the spermicidal action. Therefore the designation "vaginal jelly" or "vaginal creme" preceded by the brand or firm name would be acceptable. In each case the brand name should not be so emphasized that the following descriptive words "vaginal jelly," "jelly," "vaginal creme" or "creme" is relegated to comparative insignificant size.

**Therapeutically Suggestive Names.**—Names which carry the suggestion of a therapeutic indication, pathologic condition, disease or organism causing a disease shall be considered therapeutically suggestive. Articles bearing such names will not be accepted for New and Nonofficial Remedies, first, because they are likely to lead physicians into prescribing names instead of remedies, and second, because they tend to encourage unwarranted self-medication by the laity. Even if the name is at first apparently meaningless to the public, its meaning will soon be understood because patients soon learn the technical names applied to their diseases and symptoms.

The prohibition against therapeutically suggestive names is not applied to serums, vaccines and antitoxins, because the accepted nomenclature of the specific organisms used in their preparation makes this unavoidable and because self-medication with them is improbable.

**Rule 9.—PATENTS, TRADEMARKS, COPYRIGHTS, ETC.**—This information is important as a means of determining the legal status of medicinal articles and as an aid to their ready recognition in current publications.

*Rule 10—UNSCIENTIFIC AND USELESS ARTICLES*—The use of articles which are unessential modifications of official or established nonproprietary articles is unscientific and serves no useful purpose. The Council will not accept products which are scientifically unsound and which therefore must be considered useless or inimical to the best interests of the medical profession and the public. This class includes compounds or mixtures containing an excessive number of active ingredients, those compounds or mixtures the components of which are of no probable assistance to one another, and those articles which are of no therapeutic value.

*UNESSENTIAL MODIFICATIONS OF OFFICIAL SUBSTANCES — Imitations*—The subterfuge of obtaining proprietary rights over an official or established nonproprietary product by introducing unessential modifications also tends to confusion and abuses, and such articles will not be admitted by the Council. Essential and important modifications, however, will receive recognition. (The Council interprets the term 'established nonproprietary product' as applying to a preparation of any formula which has been published through any recognized or reasonably accessible channel of publication prior to its appropriation or modification by a manufacturer.) Duplicates of biologic products accepted under the names of the manufacturers will not be accepted under the names of the distributors.

## Tables of Approximate Equivalents of Doses, Apothecaries' and Metric Systems

<i>Weights</i>	
Apothecary or Troy	Metric
1 ounce =	30 grams (Gm.)
4 drams =	15 grams (Gm.)
2½ drams =	10 grams (Gm.)
2 drams =	8 grams (Gm.)
75 grains =	5 grams (Gm.)
1 dram =	4 grams (Gm.)
45 grains =	3 grams (Gm.)
30 grains =	2 grams (Gm.)
15 grains =	1 gram (Gm.)
10 grains =	0.65 gram (Gm.)
7½ grains =	0.5 gram (Gm.)
7 grains =	0.45 gram (Gm.)
6 grains =	0.4 gram (Gm.)
5 grains =	0.32 gram (Gm.)
4 grains =	0.25 gram (Gm.)
3 grains =	0.2 gram (Gm.)
2½ grains =	0.16 gram (Gm.)
2 grains =	0.13 gram (Gm.)
1½ grains =	0.1 gram (Gm.)
1 grain =	65 milligrams (mg.)
¾ grain =	50 milligrams (mg.)
⅔ grain =	45 milligrams (mg.)
½ grain =	32 milligrams (mg.)
⅓ grain =	24 milligrams (mg.)
¼ grain =	22 milligrams (mg.)
⅕ grain =	16 milligrams (mg.)
⅙ grain =	11 milligrams (mg.)
⅛ grain =	8 milligrams (mg.)
1/10 grain =	6.5 milligrams (mg.)
1/12 grain =	5.4 milligrams (mg.)
1/16 grain =	4 milligrams (mg.)
1/20 grain =	3.2 milligrams (mg.)
1/32 grain =	2 milligrams (mg.)
1/64 grain =	1 milligram (mg.)
1/100 grain =	0.65 milligram (mg.)
1/120 grain =	0.54 milligram (mg.)
1/160 grain =	0.4 milligram (mg.)
1/210 grain =	0.3 milligram (mg.)
1/250 grain =	0.26 milligram (mg.)
1/320 grain =	0.2 milligram (mg.)
1/640 grain =	0.1 milligram (mg.)

# Tables of Approximate Equivalents of Doses, Apothecaries' and Metric Systems—Continued

<i>Liquid Measures</i>	
Apothecary	Metric
1 pint	= 480 cubic centimeters (cc)
12 fluid ounces	= 360 cubic centimeters (cc)
8 fluid ounces	= 240 cubic centimeters (cc)
6½ fluid ounces	= 200 cubic centimeters (cc)
4 fluid ounces	= 120 cubic centimeters (cc)
3¼ fluid ounces	= 100 cubic centimeters (cc)
2 fluid ounces	= 60 cubic centimeters (cc)
1½ fluid ounces	= 50 cubic centimeters (cc)
1 fluid ounce	= 30 cubic centimeters (cc)
¾ fluid ounce	= 25 cubic centimeters (cc)
5½ fluid drams	= 20 cubic centimeters (cc)
4 fluid drams	= 15 cubic centimeters (cc)
2½ fluid drams	= 10 cubic centimeters (cc)
2 fluid drams	= 7½ cubic centimeters (cc)
80 minims	= 5 cubic centimeters (cc)
65 minims	= 4 cubic centimeters (cc)
1 fluid dram	= 3.7 cubic centimeters (cc)
50 minims	= 3 cubic centimeters (cc)
45 minims	= 2.8 cubic centimeters (cc)
32 minims	= 2 cubic centimeters (cc)
30 minims	= 1.8 cubic centimeters (cc)
20 minims	= 1.2 cubic centimeters (cc)
16 minims	= 1 cubic centimeter (cc)
15 minims	= .9 cubic centimeter (cc)
12 minims	= .75 cubic centimeter (cc)
10 minims	= .6 cubic centimeter (cc)
8 minims	= .5 cubic centimeter (cc)
5 minims	= .3 cubic centimeter (cc)
3 minims	= .18 cubic centimeter (cc)
1½ minims	= .01 cubic centimeter (cc)
1 minim	= .06 cubic centimeter (cc)

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it has sole responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

Formerly almost every country had its own system of weights and measures, a practice which resulted in much confusion. The one system which is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its unit the meter and the gram. Other systems still enjoying some popularity, albeit decreasing popularity, are the Apothecaries' or Troy weight, which is used in prescriptions; the Avoirdupois or Imperial

Weight, which is used in commerce, and the United States Apothecaries' or Wine Measure, which is not to be confused with the British Imperial System. Examples of the denominations of each system are: Apothecaries—grain, scruple (20 grains), drachm (or dram, 60 grains) Troy ounce (480 grains or 8 drachms); Avoirdupois—grain, ounce (437½ grains), pound (16 ounces or 7,000 grains) and the ton (2,000 pounds); Wine Measure—minim, fluidrachm (60 minims), Fluidounce (8 fluidrachms or 480 minims), pint (16 fluidounces), quart (32 fluidounces) For fairly accurate conversion:

1 Gm	= 15.43 grains
1 Gm	= 0.2572 dram
1 Gm	= 0.03215 Troy ounce
1 Gm	= 0.03527 Avoirdupois ounce
1 Gm	= 0.0022 Avoirdupois pound
1 grain	= 0.0648 gram (Gm)
1 grain	= 64.8 milligrams (mg)
1 dram	= 3.488 grams (Gm)
Troy or Apothecary ounce	= 31.1 grams (Gm)
1 Avoirdupois ounce	= 28.35 grams (Gm)
1 Avoirdupois pound	= 453.6 grams (Gm)
1 cubic centimeter	= 16.23 minims
1 milliliter	= 16.23 minims
1 milliliter	= 0.2705 fluid dram
1 milliliter	= 0.0338 fluid ounce
1 milliliter	= 0.00211 pint
1 milliliter	= 0.000264 gallon
1 minim	= 0.06161 cubic centimeters (cc)
1 fluid dram	= 3.966 cubic centimeters (cc)
1 fluid ounce	= 29.57 cubic centimeters (cc)
1 pint	= 471 cubic centimeters (cc)

This degree of exactness, however, is not usually necessary in figuring dosages, and round figures are used in the accompanying tables of approximate equivalents, which will be found more convenient for translating dosages from one system to the other. However, further approximation by the use of household units may cause greater errors, every one should remember that a minim does not necessarily equal one drop, a drop will vary with the viscosity and surface tension of the fluid and the nature of the dropping container. A teaspoon will hold from 4 cc. (1 fluid dram) to 7 cc., a dessert spoon from 9 to 14 cc., a tablespoon from 15 to 22 cc., a wine glass from 50 to 90 cc., a teacup from 125 to 240 cc. and a tumbler from 200 to 300 cc.

# NEW AND NONOFFICIAL REMEDIES

## CHAPTER I

### ALLERGENIC PREPARATIONS

of animals or feathers, from foods, from animal or vegetable fibers used in clothing or in upholstery, from plants and from a variety of other substances to which patients may become sensitive source for animal and of other their use has appeared rational

Allergen those that skin or m rise to rea stances in class (a) may often be determined by means of the so called patch test. Sensitivity to substances in class (b) may often be determined by the so called scratch test or by intra dermal administration

Solutions of allergens may deteriorate with age so it is necessary that they be used before the expiration of a given time determined by the regulations of the Federal Security Agency and must be stored at a low temperature. To insure sterility the council requires that liquid extracts shall be prepared so as to avoid contamination and that their sale shall be authorized by the Federal Security Agency under the law governing the sale of biologic products. The council requires that the identity of any preservative used in accepted allergenic preparations be declared on the label

*Actions and Uses*—Allergenic preparations may be used for prophylaxis in instances of hay fever or pollen asthma by employing a series of suitably graded doses of specific pollen extracts up to and through the hay fever season or for the

may be used to determine specific sensitivities to food but are not satisfactory for the treatment of these sensitivities



*Dosage.*—No uniform method of standardization has been adopted. Two methods are acceptable, first standardization by the nitrogen content of the extract, and second standardization by amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment graduated series of doses are supplied by the manufacturer. Most patients tolerate these standardized graduated doses, but in order to avoid untoward reactions at the beginning of the series, 0.02 cc. of the weakest solution should be injected intracutaneously before the series is begun. There should be no reaction or only a minimal wheal following this test.

### Bacterial Extracts

#### THE ARLINGTON CHEMICAL COMPANY

**Protein Extract:** The following protein preparations are marketed in packages of four 5 cc. vials, one each of four concentrations. In the case of food and incidental extracts these are 1:10,000, 1:5,000, 1:1,000 and 1:500. In the case of animal epidermal and fur protein extracts the concentrations are 1:100,000, 1:10,000, 1:1,000 and 1:500. Concentrations of 1:500 and 1:100 and occasionally intermediate dilutions are also marketed in 1, 2, 3, 5 and 10 cc vials.

For determining patient hypersensitivity by means of the skin test bacterial protein extracts-Arlington are supplied in vials containing 25 mg. of powdered material and in 1 cc. and 3 cc. vials containing a 1:500 solution of the protein material.

*hemolytic streptococcus (non-he*  
*Streptococcus viridans (Viridans*

These protein preparations are prepared according to a standard method, viz., growing on solid mediums, washing off with saline solution, 0.4 per cent of cresol is added and the suspension heated for one hour at from 62 to 65 C. In the case of streptococcus and pneumococcus proteins the organisms are grown in broth, centrifuged out, the bacterial paste shaken in saline solution and then treated in the same manner as described in the preceding sentence.

### Food, Epidermal and Miscellaneous Extracts

#### THE ARLINGTON CHEMICAL COMPANY

**Protein Extract:** The following protein extracts are marketed in packages of four 5 cc. vials, one each of four concentrations. In the case of food and incidental extracts these are 1:10,000, 1:5,000, 1:1,000 and 1:500. In the case of animal

epidermal and fur protein extracts the concentrations are 1 100 000 1 10 000 1 1 000 and 1 500. Concentrations of 1 500 and 1 100 and occasionally intermediate dilutions are also marketed in 1 2 3 5 and 10 cc vials

For determining patient hypersensitivity by means of the scratch test protein extracts Arlington are supplied in vials containing either 15 25 or 50 mg of the powdered protein material and in 1 cc and 3 cc vials containing a 1 500 solution of the protein material

*Abalone*<sup>3</sup> *Alaska Seal*<sup>10</sup> *Allspice*<sup>21</sup> *Almond*<sup>4</sup> *Anchovy*<sup>2</sup> *Aniseed*<sup>4</sup>  
*Apple*<sup>21</sup> *Apricot*<sup>4</sup> *Artichoke*<sup>21</sup> *Asparagus*<sup>21</sup> *Avocado*<sup>21</sup> *Badger*<sup>21</sup> *Banana*<sup>21</sup>  
*Barley*<sup>21</sup> *Barracuda*<sup>2</sup> *Barundi*<sup>21</sup> *(Chipmunk)*<sup>10</sup> *Bass (Black)*<sup>2</sup> *Bass*  
*(Sea)*<sup>2</sup> *Bay Leaves*<sup>21</sup> *Bean*<sup>21</sup> *Bear*<sup>21</sup> *Beater*<sup>10</sup> *Beef*<sup>20</sup> *Beef Serum*<sup>2</sup>  
*Beet*<sup>21</sup> *Blackberry*<sup>2</sup> *Black eyed Pea*<sup>21</sup> *Blueberry*<sup>2</sup> *Blue Fish*<sup>2</sup> *Borwood*<sup>21</sup>

Protein extracts Arlington, with two exceptions (Egg White and Wheat, Whole), are prepared as follows: A weighed amount of the dried protein material, prepared as indicated below, is suspended in twentieth-normal sodium hydroxide solution. The suspension is centrifuged and decanted and the residue, if one remains, is exhausted by successive extractions with twentieth normal sodium hydroxide solution. The extracts are combined and filtered until clear. To the filtrate is added one-fourth volume of a solution containing in each hundred cubic

content, determined according to the Kjeldahl method, by the factor 6.25; dilutions are made on the basis of the estimated protein content.

The dried protein material used in the preparation of the extracts marked 1 is prepared as follows: The hard shells are removed; nuts are ground and extracted with carbon tetrachloride or acetone to remove oils. The residue is extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 2 is prepared as follows: The edible portion is separated from the nonedible parts (scales, bones and so on) and finely ground. The material is then extracted with ten normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 3 is prepared as follows. The material is washed in acetone and ether and then ground and sifted.

The dried protein material used in the preparation of the extracts marked 4 is prepared as follows: The seeds are separated and the material chopped fine. An extract is made, sufficient tenth normal sodium hydroxide solution being used to make the mixture alkaline to litmus. The extract is filtered and neutralized and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 5 is prepared as follows: The material is chopped and after mixing with thymol is spread on trays to dry. The dried material is ground fine and extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extract marked 6 is prepared as follows: Whites of eggs are mixed thoroughly with two volumes of distilled water, heated to 80 C. and made faintly acid. The precipitate is filtered off and discarded. To the filtrate are added two and one half volumes of acetone. The precipitate formed is collected, dried and sifted.

The dried protein material used in the preparation of the extract marked 7 is prepared as follows: Egg yolks are thoroughly mixed and washed in acetone and ether to remove fat. The residue is extracted with 10 per cent sodium chloride solution. The extract is filtered off and placed in a dialyzer. The precipitate is collected, washed in distilled water, dried and sifted.

The dried protein material used in the preparation of the extract marked 8 is prepared as follows: Skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until the casein settles out. The casein is filtered off and the filtrate neutralized and concentrated in vacuo. Ammonium sulfate is added to saturation point and the precipitate redissolved in distilled water.

The solution is placed in a dialyzer and allowed to remain until the sulfate test is negative. The lactalbumin, precipitated by the addition of two and one half volumes of acetone, is collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 9 is prepared as follows. The material is dissolved in or diluted with distilled water. The solution is filtered if necessary and the protein precipitated with acetone. The precipitate is washed with acetone, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 10 is prepared as follows. The five protein fractions present in and separately prepared from wheat flour are mixed.

The dried protein material used in the preparation of the extract marked 11 is prepared as follows. Wheat flour is extracted with distilled water. The extract is collected, filtered clear and made slightly acid. It is then heated to 65 C and the precipitate filtered off, dried and sifted.

The dried protein material used in the preparation of the extract marked 12 is prepared as follows. The filtrate obtained after removing

The dried protein material used in the preparation of the extract marked 14 is prepared as follows: The residue of wheat flour remaining after the flour has been extracted with water and with 10 per cent sodium chloride solution is extracted with 80 per cent alcohol. The extract is concentrated in vacuo, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 15 is prepared as follows. Wheat flour is extracted with distilled water, 10 per cent sodium chloride solution and 80 per cent alcohol. The residue remaining is then extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 16 is prepared as follows. The material is extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the precipitate collected, dried and sifted. The filtrate is placed in a dialyser until it is salt free and then concentrated in vacuo. The concentrate is precipitated with acetone, dried and sifted. Both fractions are then mixed.

The dried protein material used in the preparation of the extract marked 17 is prepared as follows. The material is dissolved in five volumes of distilled water and then centrifuged. The supernatant liquid is discarded, the residue is dried and powdered.

The dried protein material used in the preparation of the extracts marked 18 is prepared as follows. Equal parts of the egg white and egg yolk proteins are mixed.

The dried protein material used in the preparation of the extract marked 19 is prepared as follows. Fresh skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until

The dried protein material used in the preparation of the extracts marked 21 is prepared as follows. The material is chopped thoroughly or reduced to a fine powder by grinding. Where excess oil or fat is present, this is removed by treatment with acetone or carbon tetrachloride. The material is then extracted with tenth normal sodium hydroxide solution. The extract is then neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The extracts marked 22 are prepared by the same method used in the preparation of pollen extract-Arleo (q. v.).

Exceptions to the general method of preparation: 1. Egg white protein extract-Arleo is prepared by separating the whites of fresh eggs from the yolks. The egg whites are added to an equal volume of physiologic solution of sodium chloride, passed several times through cheese cloth, and sufficient saline and "phosphate solution" (having the composition previously stated in this description) added to bring the protein content to about 1:100 (calculated). The solution is then adjusted to pH 8.3; cresol is added and the solution sterilized by Berkefeld filtration. From this point the procedure follows the general method outlined in the beginning of this description.

2. Wheat (whole) protein extract-Arleo: *Part I:* Wheat flour is extracted with 10 per cent sodium chloride solution, chloroform being used as a preservative. The extract is filtered off and dialyzed against running water until freed from salt, toluene and chloroform being used as preservatives. The solution is then centrifuged and the supernatant fraction reduced in volume in vacuo. The precipitate from dialysis is dissolved in twentieth normal sodium hydroxide solution, filtered and combined with the reduced supernatant fraction. One fourth volume of "phosphate solution" (of the composition already described) is added, the reaction of the solution adjusted to pH 8.3, and the solution filtered until clear; 0.4 per cent of cresol is added and the solution sterilized by Berkefeld filtration. The protein content is estimated by a nitrogen determination ( $N \times 6.25$ ). *Part II:* An appropriate amount of wheat flour is freed from starch, the residue dissolved in tenth normal sodium hydroxide solution, the solution filtered until clear, and its reaction adjusted to pH 8.3. Cresol 0.4 per cent is added and the solution sterilized by Berkefeld filtration. The protein content is estimated by a nitrogen determination ( $N \times 6.25$ ). Equal parts of the two products (described under "Part I" and "Part II"), by protein content, are combined. Dilutions are then made as in the general method.

## HOLLISTER-STERN LABORATORIES

**Protein Extracts Diagnostic:** Food, animal epidermal and other protein extracts are supplied for diagnostic purposes in 1 cc. ampuls fitted with capillary tube and rubber bulb and containing sufficient material for approximately 25 tests.

## LEDERLE LABORATORIES, INC.

**Allergenic Extract:** 5 cc. vials.

Extracts marketed in undiluted form:

Apple<sup>3</sup>; Apricot<sup>3</sup>; Artichoke<sup>3</sup>; Blackberry<sup>3</sup>; Blueberry<sup>3</sup>; Cantaloupe<sup>3</sup>; Cherry<sup>3</sup>; Cranberry<sup>3</sup>; Currant (Red)<sup>3</sup>; Date<sup>3</sup>; Fig<sup>3</sup>; Gooseberry<sup>3</sup>; Grape<sup>3</sup>; Grapefruit<sup>3</sup>; Huckleberry<sup>3</sup>; Juniper Berry<sup>3</sup>; Lemon<sup>3</sup>; Lime Juice<sup>3</sup>; Melon (Cantaloupe)<sup>3</sup>; Melon (Honey Dew)<sup>3</sup>; Peach<sup>3</sup>; Pear<sup>3</sup>; Pineapple<sup>3</sup>; Plum<sup>3</sup>; Pomegranate<sup>3</sup>; Prune<sup>3</sup>; Quince<sup>3</sup>; Raisin<sup>3</sup>; Raspberry (Red)<sup>3</sup>; Rhubarb<sup>3</sup>; Strawberry<sup>3</sup>; Tangerine<sup>3</sup>; Watermelon<sup>3</sup>.

Extracts marketed in undiluted form and in 1:10 dilution:

Alfalfa<sup>3</sup>; Alligator Pear<sup>3</sup>; Allspice<sup>3</sup>; Anchovy<sup>3</sup>; Artichoke (Jerusalem)<sup>3</sup>; Asparagus<sup>3</sup>; Banana<sup>3</sup>; Barley<sup>3</sup>; Bass<sup>3</sup>; Bay Leaf<sup>3</sup>; Bean (Kidney)<sup>3</sup>; Bean (Navy)<sup>3</sup>; Bean (Pea)<sup>3</sup>; Broccoli<sup>3</sup>; Brussels Sprouts<sup>3</sup>; Carrot<sup>3</sup>; Catfish<sup>3</sup>; Cauliflower<sup>3</sup>; Celery<sup>3</sup>; Chive<sup>3</sup>; Cinnamon<sup>3</sup>; Corn<sup>3</sup>; Corn (Sweet)<sup>3</sup>; Corn (Dry)<sup>3</sup>; Deer Meat<sup>3</sup>; Dill Leaves<sup>3</sup>; Duck Meat<sup>3</sup>; Egg Plant<sup>3</sup>; Endive<sup>3</sup>; Flounder<sup>3</sup>; Fluke<sup>3</sup>; Frog's Legs<sup>3</sup>; Garlic<sup>3</sup>; Ginger<sup>3</sup>; Goat Meat<sup>3</sup>; Goat Milk<sup>3</sup>; Goose Meat<sup>3</sup>; Green Pea<sup>3</sup>; Guinea Hen Meat<sup>3</sup>; Haddock<sup>3</sup>; Halibut<sup>3</sup>; Henna<sup>3</sup>; Herring<sup>3</sup>; Hops<sup>3</sup>; Horse Meat<sup>3</sup>; Horseradish<sup>3</sup>; House Dust (Mattress)<sup>3</sup>; Kale<sup>3</sup>;

Lamb<sup>1</sup> Leek<sup>1</sup> Lentil<sup>1</sup> Lettuce<sup>1</sup> Lobster<sup>1</sup> Mace<sup>1</sup> Mackerel<sup>1</sup> Milk (Cow's)<sup>1</sup> Mushroom<sup>1</sup> Nutmeg<sup>1</sup> Oat (Meal)<sup>1</sup> Okra<sup>1</sup> Olive<sup>1</sup> Onion<sup>1</sup> Orange<sup>1</sup> Oyster<sup>1</sup> Oyster Plant<sup>1</sup> Paprika<sup>1</sup> Parsley<sup>1</sup> Parsnip<sup>1</sup> Pea (Black Eyed)<sup>1</sup> Pepper (Green)<sup>1</sup> Peppermint<sup>1</sup> Perch<sup>1</sup> Pickerel<sup>1</sup> Pike<sup>1</sup> Pompano<sup>1</sup> Pork<sup>1</sup> Potato (Sweet)<sup>1</sup> Potato (White)<sup>1</sup> Pumpkin<sup>1</sup> Quail<sup>1</sup> Rabbit Meat<sup>1</sup> Rabbit Serum<sup>1</sup> Radish<sup>1</sup> Rice<sup>1</sup> Rye<sup>1</sup> Sage<sup>1</sup> Salmon<sup>1</sup> Sardine<sup>1</sup> Scallion<sup>1</sup> Scallop<sup>1</sup> Senna<sup>1</sup> Shad<sup>1</sup> Shad Roe<sup>1</sup> Shrimp<sup>1</sup> Smelt<sup>1</sup> Sole<sup>1</sup> Soy Bean<sup>1</sup> Spinach<sup>1</sup> Squab<sup>1</sup> Squash<sup>1</sup> Squid<sup>1</sup> Sturgeon<sup>1</sup> Sugar Cane<sup>1</sup> Swiss Chard<sup>1</sup> Tapaca<sup>1</sup> Tea Leaf<sup>1</sup> Terrapin<sup>1</sup> Thyme<sup>1</sup> Tobacco<sup>1</sup> Tomato<sup>1</sup> Teot (Lake)<sup>1</sup> Trout (Sea)<sup>1</sup> Tuna Fish<sup>1</sup> Turkey Meat<sup>1</sup> Turnip<sup>1</sup> Vanilla<sup>1</sup> Watercress<sup>1</sup> Wheat<sup>1</sup> Wheat<sup>1</sup> Wheatfish<sup>1</sup> Wheat (Fish)<sup>1</sup>

Extract marketed in undiluted 1 10 and 1 100 dilution  
*Horse Serum*<sup>1</sup>

Extract marketed in undiluted form and 1 100 dilution  
*Pyrethrum*<sup>1</sup>

Extract marketed in 1 10 dilution  
*Jack Bean*<sup>1</sup>

Extract marketed in dilutions representing 1 mg and 0.001 mg of nitrogen per cc  
*Silk (Silkworm)*<sup>1</sup>

Extract marketed in dilutions representing 0.5 mg and 0.05 mg of nitrogen per cc  
*Chocolate*<sup>1</sup>

Extract marketed in dilutions representing 0.2 mg and 0.1 mg of nitrogen per cc  
*Sheep Dander (Wool)*<sup>1</sup>

Extract marketed in dilutions representing 0.2 mg and 0.01 mg of nitrogen per cc  
*Cow Dander (Hair)*<sup>1</sup>

Extract marketed in dilutions representing 0.2 mg 0.01 mg and 0.001 mg of nitrogen per cc  
*Flaxseed*<sup>1</sup>

Extracts marketed in dilutions representing 0.2 mg and 0.001 mg of nitrogen per cc  
*Anise Seed*<sup>1</sup> *Canary Seed*<sup>1</sup> *Cottonseed*<sup>1</sup>

Extracts marketed in dilutions representing 0.1 mg of nitrogen per cc

*Canary Feathers (Dander)*<sup>1</sup> *Feathers (Chicken Duck Goose) (Dander)*<sup>1</sup> *Goat Dander (Hair)*<sup>1</sup> *Parrot Feathers (Dander)*<sup>1</sup> *Pigeon Feathers (Dander)*<sup>1</sup> *Turkey Feathers (Dander)*<sup>1</sup>

Extracts marketed in dilution representing 0.1 mg and 0.01 mg of nitrogen per cc

*Brazil Nut*<sup>1</sup> *Buckwheat*<sup>1</sup> *Cashew Nut*<sup>1</sup> *Chestnut (Spanish)*<sup>1</sup> *Coco-nut*<sup>1</sup> *Hazel Nut*<sup>1</sup> *Hickory Nut*<sup>1</sup> *Pecan*<sup>1</sup> *Pepper (Black)*<sup>1</sup> *Pepper (Red)*<sup>1</sup> *Pignolia Nut*<sup>1</sup> *Plantain Nut*<sup>1</sup> *Walnut (Black)*<sup>1</sup> *Walnut (English)*<sup>1</sup>

Extracts marketed in dilutions representing 0.1 mg. and 0.001 mg. of nitrogen per cc.:

*Caraway Seed*<sup>9</sup>; *Dog Dander (Hair)*<sup>4</sup>; *Egg White*<sup>4</sup>; *Kapok Seed*<sup>4</sup>; *Lycopodium*<sup>7</sup>; *Millet Seed*<sup>9</sup>; *Mustard*<sup>9</sup>; *Poppy Seed*<sup>9</sup>

Extracts marketed in dilutions representing 0.1 mg., 0.01 mg. and 0.001 mg. of nitrogen per cc.:

*Camel Dander (Hair)*<sup>4</sup>; *Cuttlefish (Bone)*<sup>4</sup>; *Hog Dander (Hair)*<sup>4</sup>; *Horse Dander (Hair)*<sup>4</sup>; *Orris*<sup>7</sup>

Extracts marketed in dilutions representing 0.1 mg. and 0.005 mg. of nitrogen per cc.:

*Almond (Nut)*<sup>1</sup>; *Peanut*<sup>1</sup>

Extract marketed in dilutions representing 0.1 mg. and 0.00001 mg. of nitrogen per cc.:

*Castor Bean*<sup>12</sup>

Extracts marketed in dilutions representing 0.01 mg. of nitrogen per cc.:

*Ascaris*<sup>1</sup>

Extracts marketed in dilutions representing 0.01 mg. and 0.001 mg. of nitrogen per cc.:

*Muskrat Dander (Hair)*<sup>4</sup>; *Raccoon Dander (Hair)*<sup>4</sup>

Extracts marketed in dilutions representing 0.05 mg. and 0.001 mg. of nitrogen per cc.:

*Cat Dander (Hair)*<sup>4</sup>; *Guinea Pig Dander (Hair)*<sup>4</sup>; *Rabbit Dander (Hair)*<sup>4</sup>

Extracts marketed in dilutions representing 0.001 mg. of nitrogen per cc.:

*Deer Dander (Hair)*<sup>4</sup>; *Fox Dander (Hair)*<sup>4</sup>; *Mouse Dander (Hair)*<sup>4</sup>; *Opossum Dander (Hair)*<sup>4</sup>; *Skunk Dander (Hair)*<sup>4</sup>

Extract marketed in dilutions representing 0.0005 mg., 0.005 mg. and 0.1 mg. of nitrogen per cc.:

*Fish Glue*<sup>10</sup>

Allergenic extracts Lederle are prepared from various substances by extraction with a buffered saline solution composed of sodium chloride 0.5 Gm., monopotassium phosphate ( $\text{KH}_2\text{PO}_4$ ) 0.0363 Gm., disodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) 0.1431 Gm., phenol 0.4 Gm., distilled water to make 100 cc. Certain of these products are standardized on the basis of their nitrogen content per unit volume. Certain others, however, do not lend themselves to such standardization and are marketed with the designations "Undiluted," "1:10 Dilution," "1:100 Dilution," etc. These "Undiluted Extracts" are ten times the strength of extracts found safe and effective in known sensitive individuals by the dermal test.

Products marked 1 are prepared by the following method. The material is shelled and ground, treated with toluene, alcohol and ether. The dry and oil-free flour is extracted with the buffered solution. The extract is dialyzed and sterilized by filtration.

Products marked 2 are prepared by the following method. The powdered whole grains are washed with toluene, alcohol and ether. The buffered saline extract of the defatted flour is dialyzed, concentrated and sterilized by filtration.

Products marked 3 are prepared by the following method. The ground material is treated with toluene and then placed immediately in the buffered extracting fluid. The extract is dialyzed and sterilized by filtration.

Products marked 4 are prepared by the following method. The material is ground in a mortar and washed with ether and alcohol. The dry residue is extracted with buffered extracting fluid. The dialyzed extract is concentrated and the amount of nitrogen per cubic centimeter of the filtered extract is determined by the Kjeldahl method.

Products marked 5 are prepared by the following method. The material is prepared by dialyzing the pressed juice at once against the buffered solution diluted (1:2) until nonirritating to normal skin. The dialyzed extract is concentrated and sterilized by filtration. If the ground material contains very little juice, it is mixed with the extracting fluid and the pressed extract is handled the same as an original juice.

Products marked 6 are prepared by the following method. The extracts are merely dilutions of the original substance in the buffered saline solution. Milk is decaseinated with rennin. The whey is dialyzed against a slightly alkaline buffered solution, concentrated and sterilized by filtration.

Products marked 7 are prepared by the following method. The powdered material is washed with toluene, alcohol and ether. The buffered saline extract of the defatted flour is dialyzed, concentrated and sterilized by filtration. The alcohol-ether treatment is exhaustive and the dialysis continued for a long time in order to insure stability of the extract and complete removal of toxic fractions present.

The product marked 8 is prepared by the following method. Raw unroasted cacao beans are ground and treated with toluene and ether until practically oil free. The resulting powder is extracted with the buffered solution. The extract is sterilized by filtration and standardized on the basis of its nitrogen content.

The product marked 9 is prepared by the following method. The powdered material is washed with toluene, alcohol and ether. After evaporation of the fat solvent it is extracted with the buffered solution. The extract is dialyzed until skin tests prove it to be no longer irritating. The final product is sterilized by filtration and standardized on the basis of its nitrogen content per cubic centimeter.

The product marked 10 is prepared by the following method. The heads of any common fish are boiled for one hour in acidified distilled water, for example, 40 pounds of fish heads in 30 liters of water with 45 cc of glacial acetic acid. The resulting extract is filtered through cloth while hot to yield 25 liters of fluid of pH 5.0. The filtrate is evaporated on a steam bath to 2 liters of thick residue, representing the stock material from which ample saline dilutions are made.

The product marked 11 is prepared by the following method. The apartment houses are dried and ether. The dry powder is buffered solution. After sterilized.

The following method. The ground material is washed with toluene, alcohol and ether until practically oil free. The resulting residue is dried and extracted with the buffered solution. The extract is boiled for three minutes for detoxification. The coagulum formed is separated at once from the extract by filtration. The toxin free extract is sterilized by filtration and standardized on the basis of its nitrogen content.

according to its nitrogen content.

**Glycerinated Allergenic Protein Extracts.** These extracts, for use exclusively by the scratch method of cutaneous



testing, are prepared in the same manner as the allergenic extracts-Lederle described above. However they contain glycerin and are much more concentrated. They are supplied in capillary tubes providing sufficient material for one scratch test.

PANKE, DAVIS & Co.

**Protein Extracts Diagnostic:** Protein extracts derived from food, plant, bacterial and other proteins, in the form of paste, the base of which is a mixture of glycerin and glycerite of starch. One part of paste represents one part of original material. The extracts afford a convenient means of carrying out the diagnostic scratch test. They are supplied in collapsible tubes containing 1.5 Gm. of material, enough for approximately 50 tests.

**Group Protein Extracts Diagnostic:** A mixture of equal parts of two or more protein extracts diagnostic-P. D. & Co., supplied in collapsible tubes containing 1.5 Gm. of the mixture. The protein constituents of each group are selected on the basis of their class relationships.

SHARP & DOHME, INC.

**Allergenic Extracts for Diagnosis:** For carrying out the scratch test these food, plant, bacterial and other protein extracts are supplied in the form of dry powder or concentrated liquid extracts. The powder form is marketed in vials containing 50 mg., sufficient for approximately 25 tests; the liquid form, in 50 per cent glycerin, is supplied in individual capillary tubes containing sufficient material for one test, and in 1 cc. vials containing enough material for one test, and in 1 cc. vials containing enough material for about 50 tests.

**Allergenic Extract:** 5 cc. vials.

Extract marketed in a dilution representing 0.00005 mg. of nitrogen per cc.:

*Castor Bean.*<sup>11</sup>

Extracts marketed in dilutions representing 0.005 mg. of nitrogen per cc.:

*Camel Hair*<sup>1</sup>, *Cat Hair*<sup>1</sup>, *Cattle Dander*<sup>1</sup>, *Cottonseed*<sup>1</sup>, *Dog Hair*<sup>1</sup>, *Egg White*<sup>1</sup>, *Egg Yolk*<sup>1</sup>, *Egg (Whole)*<sup>1</sup>, *Flaxseed*<sup>1</sup>, *Glue (Fish)*<sup>1</sup>, *Guinea-Pig Hair*<sup>1</sup>, *Hog Hair*<sup>1</sup>, *Horse Dander*<sup>1</sup>, *Kapok Seed*<sup>1</sup>, *Mustard*<sup>1</sup>, *Rabbit Hair*<sup>1</sup>, *Rat Hair*<sup>1</sup>.

Extracts marketed in dilutions representing 0.025 mg. of nitrogen per cc.

*Clave*<sup>1</sup>, *Ginger*<sup>1</sup>, *Vanilla*<sup>1</sup>, *Pyrethrum*<sup>1</sup>.

Extracts marketed in dilutions representing 0.05 mg. of nitrogen per cc.

*Allspice*<sup>1</sup>, *Almond*<sup>1</sup>, *Aniseed*<sup>1</sup>, *Bluefish*<sup>1</sup>, *Brazil Nut*<sup>1</sup>, *Buckwheat*<sup>1</sup>, *Butternut*<sup>1</sup>, *Caraway Seed*<sup>1</sup>, *Cashew Nut*<sup>1</sup>, *Chestnut*<sup>1</sup>, *Cinnamon*<sup>1</sup>, *Cocoa (Chocolate)*<sup>1</sup>, *Cocoanut*<sup>1</sup>, *Gelatin (Cattle)*<sup>1</sup>, *Goat Hair*<sup>1</sup>, *Hazel nut*<sup>1</sup>, *Hickory Nut*<sup>1</sup>, *Hops*<sup>1</sup>, *Horse-Radish*<sup>1</sup>, *Mace*<sup>1</sup>, *Nutmeg*<sup>1</sup>, *Orris*

*Root*<sup>1</sup> *Paprika*<sup>1</sup> *Parsley*<sup>2</sup> *Peanut*<sup>1</sup> *Pecan*<sup>1</sup> *Pepper (Black)*<sup>1</sup> *Pepper (Red)*<sup>1</sup> *Pimento*<sup>1</sup> *Poppy Seed*<sup>1</sup> *Rice*<sup>1</sup> *Sage*<sup>1</sup> *Squash*<sup>1</sup> *Tapioca*<sup>1</sup>,  
*Thyme*<sup>1</sup> *Walnut (Black)*<sup>1</sup> *Walnut (English)*<sup>1</sup>

Extracts marketed in dilutions representing 0.25 mg of nitrogen per cc

*Apple*<sup>1</sup> *Banana*<sup>1</sup> *Barley*<sup>1</sup> *Blackberry*<sup>1</sup> *Carrot*<sup>1</sup> *Cheese (American)*<sup>1</sup> *Cheese (Swiss)*<sup>1</sup> *Chicken Feathers*<sup>1</sup> *Corn*<sup>1</sup> *Cranberry*<sup>1</sup> *Currant*<sup>1</sup> *Duck Feathers*<sup>1</sup> *Goose Feathers*<sup>1</sup> *Grape*<sup>1</sup> *Grapefruit*<sup>1</sup> *Honey dew Melon*<sup>1</sup> *Huckleberry*<sup>1</sup> *Peach*<sup>1</sup> *Pear*<sup>1</sup> *Pepper (Sweet)*<sup>1</sup> *Pigeon Feathers*<sup>1</sup> *Plum*<sup>1</sup> *Prune*<sup>1</sup> *Pumpkin*<sup>1</sup> *Radish*<sup>1</sup> *Raisin*<sup>1</sup> *Rasp berry*<sup>1</sup> *Rice Powder (Polish)*<sup>1</sup> *Sheep Wool*<sup>1</sup> *Silk*<sup>1</sup> *Strawberry*<sup>1</sup> *Tea*<sup>1</sup> *Tobacco*<sup>1</sup> *Yeast*<sup>1</sup> *Turkey Feathers*<sup>1</sup>

Extracts marketed in dilutions representing 0.5 mg of nitrogen per cc.

*Anchovy*<sup>1</sup> *Apricot*<sup>1</sup> *Artichoke*<sup>1</sup> *Bass (Sea)*<sup>1</sup> *Bean (Kidney)*<sup>1</sup> *Bean (Lima)*<sup>1</sup> *Bean (Navy)*<sup>1</sup> *Bean (Soy)*<sup>1</sup> *Bean (String)*<sup>1</sup> *Beef*<sup>1</sup> *Beet*<sup>1</sup> *Brussel Sprouts*<sup>1</sup> *Butterfish*<sup>1</sup> *Cabbage*<sup>1</sup> *Cantaloupe*<sup>1</sup> *Carp*<sup>1</sup> *Cashew*<sup>1</sup> *Cauliflower*<sup>1</sup> *Chicken*<sup>1</sup> *Chickory*<sup>1</sup> *Clam*<sup>1</sup> *Codfish*<sup>1</sup> *Coffee*<sup>1</sup> *Crab*<sup>1</sup> *Date*<sup>1</sup> *Duck*<sup>1</sup> *Eggplant*<sup>1</sup> *Fig*<sup>1</sup> *Garlic*<sup>1</sup> *Goose*<sup>1</sup> *Haddock*<sup>1</sup> *Halibut*<sup>1</sup> *Herring*<sup>1</sup> *Lactalbumin (Cow's Milk)*<sup>1</sup> *Lamb*<sup>1</sup> *Lemon*<sup>1</sup> *Lentil*<sup>1</sup> *Lettuce*<sup>1</sup> *Lime*<sup>1</sup> *Lobster*<sup>1</sup> *Macarrel*<sup>1</sup> *Mushroom*<sup>1</sup> *Oats*<sup>1</sup> *Okra*<sup>1</sup> *Olive*<sup>1</sup> *Onion*<sup>1</sup> *Orange*<sup>1</sup> *Oyster*<sup>1</sup> *Perch*<sup>1</sup> *Pike*<sup>1</sup> *Pineapple*<sup>1</sup> *Salmon*<sup>1</sup> *Sardine*<sup>1</sup> *Scall*<sup>1</sup> *Sole (Flounder)*<sup>1</sup> *Spinach*<sup>1</sup> *Tuna Fish*<sup>1</sup> *Turkey*<sup>1</sup> *Tu*<sup>1</sup>

Extracts marketed in dilutions representing 1.0 mg of nitrogen per cc

*Asparagus*<sup>1</sup> *Celery*<sup>1</sup> *Cherry*<sup>1</sup> *Cucumber*<sup>1</sup> *Potato (Sweet)*<sup>1</sup> *Potato (White)*<sup>1</sup> *Watermelon*<sup>1</sup>

Extract marketed in a dilution representing 0.75 mg of nitrogen per cc

*Feathers Mixed (Chicken Duck and Goose)*<sup>1</sup>

Other extracts are

*House Dust Allergenic Extract*<sup>1</sup> is furnished in three strengths representing 100 1 000 or 5 000 protein units<sup>1</sup> per cc

\* The protein unit is fixed at 0.00001 mg protein nitrogen. The protein nitrogen in the extract is determined by the Kjeldahl method after phosphotungstic acid precipitation of the protein fraction.

*Whole Milk (Cow) Allergenic Extract*<sup>1</sup> represents a 1:2 dilution of Whole Milk (Cow)

*Horse Serum Allergenic Extract*<sup>1</sup> represents a 1:20 dilution of Horse Serum

Allergenic Extracts Mulford are prepared by extracting various substances with buffered salt solution consisting of monopotassium phosphate ( $\text{KH}_2\text{PO}_4$ ) 0.363 Gm disodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) 1.43 Gm and sodium chloride ( $\text{NaCl}$ ) 5 Gm. in 1 liter of distilled water containing 0.4 per cent of phenol.

Products marked 1 are prepared for extraction as follows. The crude material is ground as fine as possible. The powder or flour is treated with carbon tetrachloride and ether. The washings are discarded and the residue is dried. The dried residue is extracted with buffered salt solution under toluene for 72 hours. The extract is dialyzed against buffered salt solution and astringed.

Products marked 2 are prepared for extraction as follows: The fruits and vegetables are ground as fine as possible and dialyzed against running tap water. The dialyzed pulp and juice are dried and extracted with buffered salt solution for 72 hours. Sterilization is then carried out by candle filtration.

Products marked 3 are prepared for extraction as follows: The muscle fibers, after the removal of fat and tendons, are ground as fine as possible. The ground muscle is washed with toluene until free from fats and oils. The toluene washings are discarded. The ground defatted meat is extracted under toluene with buffered salt solution. The extract is dialyzed and sterilized.

Products marked 4 are prepared for extraction as follows: The feathers or hair are washed with ether and the suspended particles of dander are collected by filtration. The dried material is extracted under toluene with buffered salt solution from one to three days at room temperature.

Preparations marked 5 are prepared for extraction as follows: The yolk of an egg is separated from the white in a sterile manner. One part of egg white, or egg yolk, is diluted with four parts of sterile buffered salt solution.

Lactalbumin, marked 6, is prepared for extraction as follows: The fat from 1 liter of milk is removed by centrifugation. The fat free milk is saturated at 30 C. with magnesium sulfate, which precipitates the caseinogen and lactoglobulin. The filtrate is acidified with acetic acid so that the content of the acid is 1 per cent. The precipitate is filtered off, pressed out, and dissolved in water, the solution is neutralized and dialyzed. (*Practical Organic and Biochemistry*, R. H. A. Plimmer, p. 446)

Milk, marked 7, is prepared for extraction as follows: One liter of fresh nonheated milk, from which the fat has been removed by centrifugation, is mixed with 3 cc. of 1 per cent rennin solution and placed in a water bath at 37 C. for one half hour. The precipitated casein is removed by straining through a sterile towel. The filtrate is neutralized with saturated solution of sodium bicarbonate, and sterilized by filtration (*J. Immunol.* 16:2, 1928).

Dust, marked 8, is prepared for extraction as follows: The dust is washed with ether and extracted under toluene with a mixture of two parts of alkaline extracting fluid (2.5 Gm. of sodium bicarbonate and 5 Gm. of sodium chloride in 1 liter of distilled water) and one part of buffered salt solution saturated with carbon dioxide. The extract is then concentrated by a rapid freezing and dehydrating process (lyophilization). The concentrated extract is then dialyzed against the alkaline extracting fluid just described, carbon dioxide being passed through the solution constantly during the period of dialysis. After dialysis is complete, sterilization is carried out by candle filtration and the final house dust extract standardized in terms of protein nitrogen units.

Horse serum, marked 9, is prepared for extraction as follows: Normal horse serum containing 0.4 per cent of phenol as a preservative is used.

Glue, marked 10, is prepared for extraction as follows. Glue is extracted with buffered salt solution.

Castor Bean, marked 11, is prepared for extraction as follows: The material is ground and washed with toluene and ether until the washings are colorless. The residue is extracted with buffered salt solution for 72 hours at room temperature. The extract is boiled for 3 minutes and filtered through a Mandler candle.

Allergic Extracts Mulford are tested and standardized in terms of "nitrogen units." The nitrogen unit has been arbitrarily chosen as 0.00016 mg. of total nitrogen. Clinical tests are also conducted on sensitive individuals. The extracts employed for diagnosis are supplied in a concentration based on a test dose of 0.02 cc. injected intradermally. The extracts used for desensitization are made up to a concentration of five times the test dose. With the exception of Horse Serum allergic extract, Whole Milk (Cow) allergic extract, and House Dust allergic extract all extracts are labeled to indicate the amount of nitrogen represented in each cubic centimeter.

## Fungus Extracts

## ABBOTT LABORATORIES

Fungus Extract 2 cc 5 cc and 30 cc vials

*Alternaria spp Aspergillus fumigatus Aspergillus niger Group Cephalothecium roseum Hormodendrum spp Monilia staphilia Mucor spp Penicillium cubenum Ustilago zeae (Corn Smut) Yeast*

The yeast extract is prepared from dried brewers yeast the *Alternaria spp* extract is prepared from the dried mass of spores with its supporting mycelium the other extracts are prepared from the dried spores alone The material is extracted at room temperature with a menstruum consisting of equal volumes of glycerin and a solution containing sodium chloride 5 Gm and sodium bicarbonate 27 Gm in distilled water 1000 cc for from four to five days and is clarified and sterilized by Berkefeld filtration The finished liquid is a 5% W/V extract of the dried fungus material each cubic centimeter representing 0.05 Gm of dried material

## Pollen Extracts

## ABBOTT LABORATORIES

Concentrated Pollen Extract 2 cc and 5 cc vials

U S patent 1977803 (Oct 23 1934 expires 1951)

*Annual Sage Arizona Ash Ash Beemuda Grass Black Walnut Biennial Sage Blue Grass Box Elder Burweed Marsh Elder Canada Blue Grass Cocklebur Corn Cosmos Coastal Sagebrush Cottonwood Crab Grass Dandelion English Plantain Elm False Ragweed Giant Ragweed Goldenrod Goose Grass Hemp Hickory Johnson Grass Lamb's Quarters Marsh Elder Mixed Grass (Blue Grass Timothy Orchard Grass Red Top and Sweet Vernal Grass in equal parts) Mixed Ragweed (Ambrosia elatior and Ambrosia trifida) Mountain Cedar Mugwort Oak Concentrated Orchard Grass Or Eye Daisy Palmer's Amaranth Plantain Prairie Sage Quailbush Redroot Pigweed Red Sorrel Redtop Russian Thistle Sagebrush Short Ragweed Slender False Ragweed Southern Ragweed Spiny Amaranth Sudan Grass Sunflower Sweet Vernal Grass Sycamore Timothy Western Ragweed Western Water Hemp Yellow Dock Yellow Fox Tail*

Concentrated pollen extracts Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water The extract is clarified and sterilized by filtration The finished liquid is a 3 per cent extract of the dried pollen each cubic centimeter representing 0.03 Gm of dried pollen (30 000 units)

Pollen Extract Extracts marketed in the following forms

Treatment sets of 16 vials containing for each consecutive dose (1 to 16 inclusive) 10 20 40 70 100 200 400 700 1000 1500 2000 3000 4000 5000 and 5000 pollen units respectively accompanied by a vial containing three 0.025 Gm (3/8 gram) capsules ephedrine hydrochloride

U S patent 1977803 (Oct 23 1934 expires 1951)

*Mixed Grass (Timothy June Grass Orchard Grass Red Top and Sweet Vernal Grass in equal proportions) Ragweed (Ambrosia elatior and Ambrosia trifida)*

Extracts marketed in special dilution sets

*Mixed Ragweed Pollen Extract Decimal Dilution Set* A mixture of equal parts of short and giant ragweed pollen extract marketed in packages of four vials containing respectively 3 cc of a 1:10 000 dilution

(100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter), 5 cc. of a 1:100 dilution (10,000 pollen units per cubic centimeter), and 5 cc. of a 1:10 dilution (100,000 pollen units per cc.)

**Mixed Grass Pollen Extract, Decimal Dilution Set:** A mixture of equal parts of June grass, timothy, orchard grass, redtop, and sweet vernal grass pollen extracts, . . . . . cc.  
 5 cc. of a 1:10, . . . . . cc.  
 of a 1:1,000 dil . . . . . of a  
 1:100 dilution . . . . . of a  
 1:100 dilution (10,000 pollen units per cc.)

Pollen extracts Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units). Dilutions are prepared with additional menstruum.

**Pollen Extracts Diagnostic:** For skin testing the extracts are supplied in vials of 3 and 50 capillary tubes, each tube providing sufficient material for one scratch test.

### THE ARLINGTON CHEMICAL COMPANY

**Pollen Extract:** The following extracts are marketed in sets of five vials representing graduated concentrations, namely, 1 in 10,000, 1 in 5,000, 1 in 1,000, 1 in 500 and 1 in 100, respectively.

For diagnostic purposes concentrated solutions of the extracts are supplied in capillary tubes containing sufficient material for one test and in 1 cc vials containing enough material for approximately 15 tests. Dry pollens suitable for use in carrying out diagnostic scratch tests are supplied in vials containing 50 mg.

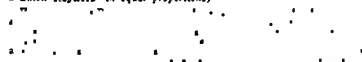
*Acacia (Scop), Alfalfa, Arizona Ash, Arizona Cottonwood, Arizona Walnut, Ash, Aster, Bermuda Grass; Birch Mixture (White Birch, Black Birch and Yellow Birch, in equal parts); Birch, Box Elder; Burning Bush; Burr Ragweed, Burroed, California Mugwort; California Walnut (Black), Carlessweed, Carpet Sage, Cherry; Cocklebur, Cosmos, Clover, Corn, Dahlia, Daisy, Dandelion; Dock; Elm; Fleabane (Common), Golden Glow, Golden Rod; Goosefoot, Grass Mixture No. 1 (Timothy, June Grass, Orchard Grass and Red Top, in equal parts), Grass Mixture No. 2 (Timothy, 40 per cent, June Grass, Orchard Grass, Red Top and Sweet Vernal Grass, each 15 per cent); Grass Mixture No. 3 (Bermuda Grass and Johnson Grass, in equal parts); Greasewood, Hickory; Hill Sage, Indian Rice, Indian Wormwood, Johnson Grass, June Grass (*Poa pratensis*), Live Oak, Locust, Maple Mixture (Red Maple, Ash-Leaved Maple, Norway Maple and Sugar Maple, in equal parts), Maple, Marsh Elder, Meadow Fescue; Mexican Tea, Mountain Cedar, Mugwort, Narcissus, Oak Mixture (White Oak, Red Oak, Black Oak and Swamp Oak, in equal parts), Oak; Oat Grass; Olive, Orach, Orchard Grass, Pigweed, Pine; Plantain; Poplar; Prairie Ragweed, Prairie Sage, Privet, Ragweed Dwarf and Giant Mixture (equal parts of each), Ragweed Mixture Plus Burweed Marsh Elder, Ragweed (*Ambrosia trifida*), Ragweed (*Ambrosia artemisiifolia*), Red Fescue, Redtop, Rose, Russian Thistle, Rye, Rye Grass; Sage-Brush; Sea Blite; Shad Scale, Slender Ragweed, Spiny Amaranth, Sunflower; Sweet Clover, Sweet Vernal Grass, Sycamore, Thistle; Timothy, Velvet Grass, Walnut; Western Cottonwood, Western Ragweed (Giant), Western Water Hemp, Wild Sunflower, Winter Fat Pollen, Willow; Yellow Daisy*

Pollen extracts Arlington are prepared by the method of Walker (*Am J M Sc* 157 402 [March] 1919). To 0.5 Gm. of the dry pollen is added 44 cc. of sterile physiologic solution of sodium chloride and the mixture is shaken thoroughly at frequent intervals for twenty-four hours. Sufficient absolute alcohol (7 cc.) is then added to make the alcohol content 14 per cent. The mixture is thoroughly shaken at frequent intervals for twenty-four hours after which it is centrifugalized at high speed and the supernatant fluid is drawn off with a pipette. This liquid represents 1 part of pollen in 100 parts of a solvent which consists of about 14 per cent alcohol added to isotonic solution of sodium chloride. This 1 in 100 solution is used as stock and from it other dilutions such as 1 in 500, 1 in 1,000, 1 in 5,000 and 1 in 10,000 are made. Cresol is added as a preservative.

### BARRY ALLERGY LABORATORY, INC.

**Allergenic Extract.** The following extracts are marketed in complete treatment set packages consisting of four vials representing graduated concentrations namely, 1 in 33⅓, 1 in 500, 1 in 10,000 and 1 in 100,000 respectively and in single vial packages containing 5 cc. of a 1 in 33⅓ solution, 0.5 per cent phenol (phosphate buffer pH 7.4) used as preservative.

*Gross Mixture (Spring) (June Grass Timothy Red Top Sweet Vernal Grass and Orchard Grass in equal proportions) Ragweed (Large and Small Ragweed in equal proportions)*



Concentration. The extract is subjected to bactericidal treatments and is tested for sterility before dilution, after dilution and after filling as required by the National Institute of Health. The finished liquid contains 8 per cent of glycerin and 0.4 per cent of cresol. The pollen unit corresponds to 0.001 mg. of dried pollen.

### CUTLER LABORATORIES

**Pollen Extract.** The following extracts are marketed in complete treatment set packages consisting of three vials representing graduated concentrations namely, 1 in 10,000, 1 in 500 and 1 in 33⅓ respectively, and in single vial packages containing 5 cc. of a 1 in 33⅓ solution, 0.5 per cent phenol (phosphate buffer pH 7.4) used as preservative.

*Acacia Alder Alfalfa Alkali Rye Grass Alkali Weed All Scale Almond Annual Blue Grass Annual Salt Bush Ash Aspen Bent Grass Bermuda Grass Birch Black Walnut Box Elder Bract Scale Bromo Grass Branch Grass Burning Bush Canada Blue Grass Canary Grass Careless Weed Chopped Broom Chest Grass Chrysanthemum Clover Coast Sagebrush Cocklebur Common Ragweed Coreopsis Corn Cosmos Cottonwood Cultivated Rye Curly Dock Dahlia Dandelion Date Deodar Cedar Elm English Walnut Euca-lyptus False Coastal Ragweed False Ragweed Field Oats Field Wheat Giant Ragweed Goldenrod Greasewood Hops Incense Cedar Johnson Grass June Grass Koehlers Grass Lambs Quarters Locust, Marsh Elder Mesquite Mexican Tea Monterey Cypress Mountain Cedar Mountain Sagebrush Mustard Mustard Oak Other Orchard Grass Pasture Sagebrush Pecan Perennial Rye Grass Pockweed Plain Poley Weed Prairie Sagebrush Privet Quack Grass Rabbit Brush*

*Red Root Pigweed; Red Top Grass; Rose; Russian Thistle; Rye Grass, Sagebrush; Salt Grass; Shad Scale; Shasta Daisy; Sheep Sorrel; Slender Wheat; Southern Ragweed; Sparscale; Spiny Amaranth; Sugar Beet, Sunflower; Sweet Vernal; Sycamore; Tall Oat Grass; Timothy; Velvet Grass, Western Ragweed; Western Water Hemp, White Valley Oak; Wild Oat; Willow; Yellow Pine.*

2  
cc  
bu  
N

Gm.  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  per liter). Two per cent of this buffer solution is used to get a final pH (after sterilization) of 7.4

The pollen extract is clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cc. representing 0.03 Gm. of dried pollen. Dilutions containing the equivalent of 0.003 Gm. of pollen per cc. and dilutions containing the equivalent of 0.001 Gm. of pollen per cc. are prepared by diluting the 3 per cent extract with the same solution as was used for extracting

## HOLLISTER-STIER LABORATORIES

**Pollen Extract:** The following extracts are marketed in treatment sets of four vials containing, respectively 10, 100, 1,000 and 10,000 units per cubic centimeter accompanied by one vial of sterile distilled water for diluting the extract; in treatment sets of thirty vials, twenty containing, respectively, 1, 2, 3, 5, 8, 12, 20, 30, 50, 80, 100, 150, 200, 300, 400, 500, 600, 700, 850, 1,000 and ten each containing 1,000 units, accompanied by thirty vials of distilled sterile water for diluting the extract.

For diagnostic purposes these pollen extracts are marketed in individual capillary tubes providing sufficient material for one test and in ampuls containing 0.5 cc. The ampuls are fitted with a capillary tube and rubber bulb and provide sufficient extract for eight to ten tests.

*Alder, Aspen, Atriplex, Awless Brome Grass, Blue Bunch Grass; Box Elder, Canada Blue Grass, Cheat, Common Sagebrush, Crested Koeleria, Dandelion, Eastern Ragweed, English Plantain; Giant Poverty Weed, Kentucky Blue Grass, Lamb's Quarters, Mugwort; Orchard Grass, Perennial Rye Grass, Quack Grass; Redtop; Redroot Pigweed; Russian Thistle, Sandberg's June Grass, Sheep Sorrel; Spring Birch, Timothy, Velvet Grass, Western Ragweed, Willow.*

Pollen extracts Hollister-Stier are prepared by extracting the dried pollen with a menstruum composed of 50 per cent of glycerin, 5 per cent of sodium chloride and 45 per cent distilled water. The extract is clarified by Seitz filtration. The finished liquid is a 1 per cent extract of the dried pollen, each cubic centimeter representing 10,000 pollen units, 1 unit corresponding to 0.001 mg. of dried pollen.

## LEDERLE LABORATORIES, INC.

**Concentrated Pollen Antigen:** The following concentrated pollen antigens are marketed in packages: Complete Series, fifteen syringes containing, respectively, 2.5, 5, 10, 20, 35, 60, 100, 165, 275, 450, 750, 1,200, 1,800, 2,400 and 3,000 pollen units

Series A: five syringes containing for each consecutive dose (1 to 5 inclusive) 2.5, 5, 10, 20 and 35 pollen units, respectively

Series B five syringes containing for each consecutive dose (6 to 10 inclusive) 60 100 165 275 and 450 pollen units respectively

Series C five syringes containing for each consecutive dose (11 to 15 inclusive) 750 1200 1800 2400 and 3000 pollen units respectively

Series D five syringes each containing 3000 units

Series E five syringes each containing 6000 units

Series F five syringes containing respectively 3600 4200 4800 5400 and 6000 pollen units

For diagnosis by the scratch method the extracts are supplied in individual capillary tubes containing enough material for one test

*Mixed Grasses (June Grass Orchard Grass Sweet Vernal Grass Red Top and Timothy in equal parts) Ragweed Combined (Common and Giant Ragweed in equal parts)*

Concentrated pollen antigens Lederle are prepared by extracting dried pollen in a quantity of extracting fluid calculated to give 30 000 pollen units per cubic centimeter according to a nitrogen-determination previously done on a sample of each stock of dried pollen (the pollen unit having been arbitrarily chosen as the equivalent of 0.00001 mg of total nitrogen). Extraction is carried out as follows: Pollen is thoroughly mixed with an aqueous solution containing 50 per cent glycerin 0.5 per cent sodium chloride 0.27 per cent sodium bicarbonate and 0.45 per cent phenol for two hours at room temperature and after another thorough mixing stored overnight in the ice box (35°C). After the extracting period the mixture is again thoroughly shaken and is immediately filtered.

**Pollen Antigen.** The following pollen antigens are marketed in packages of three 3 cc vials containing 100 1500 and 20 000 pollen units per cubic centimeter respectively and also in individual vials of each unitage.

For diagnosis by the scratch test method the extracts are supplied in individual capillary tubes containing enough material for one test.

*Acacia Annual Salt Bush Ash Beech Bermuda Grass Birch Black Walnut Coreless Weed Cocklebur Cottonwood Giant Ragweed Green Sage Hickory Johnson Grass June Grass (Poa pratensis) Lamb's Quarters Marsh Elder Mesquite Mountain Cedar Mugwort Oak Olive Orchard Grass Pasture Sage Pecan Perennial Rye Grass Plantain Paplar Prostrate Pigweed Rabbit Bush Ragweed (Ambrosia elatior) Ragweed Combined (Common and Giant Ragweed in equal parts) Redroot Pigweed Redtop Russian Thistle Sagebrush Shad Scale Sleep Sarsel Sleider Ragweed Southern Ragweed Spiny Amaranth Summer Cypress Sweet Vernal Grass Syca more Timothy Western Water Hemp Western Ragweed Yellow Dock*

The following mixtures of pollen antigens are marketed in the package forms designated in Series A B C D E and F

*Mixed Grasses (June Grass Orchard Grass Sweet Vernal Grass Red Top and Timothy in equal parts) Ragweed Combined*

Series A five vials containing for each consecutive dose (1 to 5 inclusive) 25 5 10 20 and 35 pollen units respectively and five vials of sterile diluent with which to make the proper dilution of each dose



Series B: five vials containing for each consecutive dose (6 to 10, inclusive) 60, 100, 165, 275 and 450 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series C: five vials containing for each consecutive dose (11 to 15, inclusive) 750, 1,200, 1,800, 2,400 and 3,000 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series D: five vials each containing 3,000 pollen units and five vials of sterile diluent with which to make the proper dilution of each dose.

Series E: five vials each containing 6,000 pollen units and five vials of sterile diluent with which to make the proper dilution of each dose.

Series F: five vials containing for each consecutive dose (16 to 20, inclusive) 3,600, 4,200, 4,800, 5,400 and 6,000 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Complete Series: packages containing the 15 doses described in Series A, B and C.

Pollen antigens Ledette are prepared by extracting dried pollen in a quantity of extracting fluid calculated to give 30,000 pollen units per cubic centimeter, according to a nitrogen determination previously done on a sample of each stock of dried pollen (the pollen unit having been arbitrarily chosen as the equivalent of 0.00001 mg. of total nitrogen). Extraction is carried out as follows: Pollen is thoroughly mixed with an aqueous solution containing 50 per cent glycerin, 0.5 per cent sodium chloride, 0.27 per cent sodium bicarbonate and 0.45 per cent phenol, for two hours at room temperature; and, after another thorough mixing, stored overnight in the ice box (35°C). After the extracting period, the mixture is again thoroughly shaken and is immediately filtered.

## THE NATIONAL DRUG CO.

**Allergenic Extract:** The following pollen extract is marketed in 5 cc ampul-vial packages representing, respectively, 2,500, 5,000, 10,000 and 25,000 nitrogen units per cubic centimeter, and in 1 cc syringe packages representing 100 nitrogen units per cubic centimeter.

For determining patient hypersensitivity by means of the scratch test the extracts are supplied in individual capillary tubes containing sufficient material for one test.

The following preparations are marketed in 5 and 15 cc ampul-vial packages representing, respectively, 2,500, 5,000, 10,000 and 25,000 nitrogen units per cubic centimeter:

*Ragweed (Giant and Dwarf Ragweed in equal parts), Mixed Grass (Timothy, 75 per cent, June Grass, Orchard Grass, Red Top, Rye, and Sweet Vernal Grass, each 5 per cent)*

Allergenic extracts are prepared by the following method: The pollen is weighed and extracted with ether. After removal of the ether the material is mixed with the extracting liquid consisting of a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0.4 per cent of phenol and then covered with toluene. After four days, during which time

the mixture is shaken once or twice daily, the supernatant fluid is decanted and the sediment mixed with a second portion of extracting fluid. As soon as the sediment has settled, the supernatant fluid is decanted and is then subjected to nitrogen content on a basis of

### SHARP & DOHME, INC.

**Pollen Extract.** The following pollen extracts are marketed in 5 cc. vials containing 20,000 pollen units per cubic centimeter, and are also supplied in complete treatment packages consisting of one 2 cc vial containing 500 pollen units per cubic centimeter and one 10 cc vial containing 10,000 pollen units per cubic centimeter.

*Acacia, Alder, Alfalfa, Annual Sage, Annual Salt Bush, Apple, Arizona Ash, Arizona Walnut, Ash Tree, Aster, Barnyard Grass, Bermuda Grass, Birch, Blue Birch, Boneset, Box Elder, Bromo Grass, Burning Bush, Burnweed, Marsh Elder, California Mugwort, Canada Blue Grass, Canary Grass, Careless Weed, Cedar Tree, Chrysanthemum, Coast Sage, Cocklebur, Corn Cosmos, Cottonwood Tree, Crab Grass, Dahlia, Daisy, Dandelion, Dock, Dragon Sage, Elm Tree, English Plantain, False Ragweed, Fescue Grass, Golden Glow, Goldenrod, Hickory Tree, High Ragweed, Johnson Grass, June Grass, Koeleria Grass, Lamb's Quarters, Live Oak, Low Ragweed, Maple, Marsh Elder, Mesquite, Mexican Tea, Mock Orange, Mountain Cedar, Mugwort, Oak*

*Grass Mixture (Timothy, June, Orchard, Sweet Vernal, and Red Top Grass, in equal proportion), Grass Mixture (Pollens of Southwestern Grasses—Bermuda Grass and Johnson Grass 30 per cent each, June Grass and Timothy Grass 20 per cent each)*

The pure dry pollen is extracted with an extracting fluid containing equal parts of double strength Coca's fluid (1 per cent sodium chloride and 0.5 per cent sodium bicarbonate) at room temperature (20 C) for 72 hours. During extraction, the extract is kept saturated with carbon dioxide. The pollen residue is removed by centrifugation. The stock extract contains 100,000 pollen units per cc. Dilutions are then made using isotonic phosphate buffered saline. The diluted extract is sterilized by Berkefeld filtration, and tested for sterility and safety. The finished product contains 0.4 per cent phenol as a preservative. Standardization is on the basis of pollen units, one pollen unit being equivalent to 0.001 mg of pure pollen.

**Lyovac Pollen Extracts-Mulford.** The following Lyovac pollen extracts-Mulford are supplied in complete treatment packages of four vacule ampul vials containing the lyophilized extract, and four ampuls, each containing 2 cc of sterile distilled water with 0.35 per cent phenol as preservative, also in supplementary treatment packages of one vacule ampul vial containing the lyophilized extract and one ampul containing 2 cc of sterile distilled water with 0.35 per cent phenol as preservative. After restoration of the lyophilized

extract to the fluid state each of the four vacule ampul-vials in the complete treatment package contains 2 cc. of pollen extract solution providing, respectively, 400, 4,000, 20,000 and 20,000 pollen units per cubic centimeter. Similarly the single vacule ampul-vial in the supplementary treatment package contains 2 cc of pollen extract solution providing 20,000 pollen units per cubic centimeter:

*Timothy Lycopac Pollen Extracts, Grass Mixture (timothy, June grass, orchard grass, sweet vernal grass and red top, 20 per cent each) Lycopac Pollen Extract, Ragweed (high ragweed and low ragweed, 50 per cent each) Lycopac Pollen Extract.*

Matured pollens are thoroughly dried, separated from extraneous material and defatted by ether extraction. The defatted pollen is extracted for twenty four hours at a temperature of 5 C. with a buffered saline solution containing dibasic sodium phosphate and acid potassium phosphate and adjusted to a pH of 7.4. The extracts are sterilized by candle filtration and standardized on the basis of their protein nitrogen content. When adjusted to the desired strength, the pollen extracts are filled into vacule ampulvials and processed therein. By means of the lyophile process the freshly prepared extracts are rapidly frozen at sub zero temperatures, dehydrated under vacuum and preserved under vacuum in the market container. The extracts are standardized on the basis of their protein nitrogen content and their potency is expressed in terms of the pollen unit, which is equivalent to 0.000003 mg. of protein nitrogen.

For diagnosis by means of the scratch test the extracts are supplied in individual capillary tubes containing sufficient material for one test. Dried pollens are also supplied for diagnostic purposes in vials containing 50 mg., enough for about 25 tests.

### E. R. SQUIBB & SONS

**Pollen Extract:** The following pollen extracts are marketed in treatment set packages of three 35 cc. vials, representing respectively 100, 1,000 and 10,000 protein nitrogen units per cubic centimeter; in 5 cc and 20 cc. individual vial packages representing 10,000 protein nitrogen units per cubic centimeter, and in 5 cc and 20 cc individual vial packages representing 25,000 protein nitrogen units per cubic centimeter.

For diagnosis by means of the scratch test, the extracts are supplied in concentrated form in individual capillary tubes containing enough material for one test.

*Grasses Northern Combined (June Grass, Red Top, Sweet Vernal Grass, Orchard Grass and Timothy in equal parts) Grasses Southern Combined (Bermuda Grass, Johnson Grass, June Grass, Orchard Grass and Red Top in equal parts) Ragweed Combined (Giant and Dwarf Ragweed in equal parts) Ragweed and Cocklebur Combined (Giant Ragweed, Dwarf Ragweed and Cocklebur in equal parts)*

The following pollen extracts are marketed in 5 cc. vials containing 10,000 protein nitrogen units per cubic centimeter:

*Annual Blue Grass, Ash, Bermuda Grass, Birch (Black, Gray and White Birch in equal parts), Black Walnut, Burning Bush, Burweed, Marsh Elder, California Black Walnut, Careless Weed, Cocklebur, Corn, Cottonwood (Wecklax Poplar), Dandelion, Dock (Butter Dock and Yellow Dock in equal parts), Elm, English Plantain, False Ragweeds Combined (False Ragweed and Slender Ragweed in equal parts), Goldenrod, Hickory (Black Hickory and White Hickory in equal parts);*

Johnson  
Silver  
Elder  
Hings  
(Doun)

• • • • •

in equal parts)

Pollen extracts Squibb are prepared by the following method. The pollen is weighed and extracted with 1 per cent sodium chloride solution for twelve hours. The protein nitrogen in the extract is determined by the Kjeldahl method after phosphotungstic acid precipitation of the protein fraction and the extract is diluted with glycerin and 1 per cent sodium chloride solution until the final volume contains 50 per cent of glycerin. The solution is then filtered through a Berkefeld filter and the filtrate is tested for sterility and diluted so that each dosage form contains the declared quantity of pollen nitrogen units. The protein nitrogen fraction of 0.00001 mg. is one protein nitrogen unit.

## U S STANDARD PRODUCTS CO

**Allergenic Extracts.** The following pollen extracts are supplied in 5 cc vials containing 20,000 units per cubic centimeter. In addition, two of the products (Grasses Combined and Ragweed Combined) are marketed in single treatment set packages of three vials, containing respectively 100, 1,000 and 10,000 units per cubic centimeter and accompanied by a vial containing 2 cc of epinephrine hydrochloride solution 1:1,000. Five tenths per cent of phenol is used as preservative.

For the diagnostic scratch test highly concentrated pollen extract solutions are supplied in individual capillary tubes containing sufficient material for one test.

*Alder (Tag)* A • • • • •

*Box Elder* Burns

*Chrysanthemum*

*mae Cottonwood*

*English Plantain*

*Grass Orchard C*

*equal parts) John*

*Elder Mugwort*

*root) Pine (Wh*

*(Common) Ragw*

*Ragweed (Wester*

*in equal parts) Red Oak Red Top Russian Thistle Eye Grass Sage*

*(Common) Sage (Prairie) Sheep Sorrell Sudan Grass Sunflower*

*Sweet Vernal Grass Sycamore Timothy Velvet Grass Blunt (Black)*

*Water Hemp (Western) Wheat (Field) White Ash White Oak Yellow*

*Dock*

The following product is supplied in 5 cc vials representing 30,000 pollen units per cubic centimeter and in packages of four 5 cc vials representing respectively, 100, 1,000, 10,000 and 10,000 pollen units per cubic centimeter.

*Ragweed Combined (Giant and Common Ragweed in equal parts)*

The following product is supplied in 5 cc vials representing 30,000 pollen units per cubic centimeter:

*Grasses Combined (Bermuda, June Grass, Orchard Grass, Red Top, Sweet Vernal Grass and Timothy in equal parts).*

Prepared by extracting the dried pollen with a menstruum containing 67 per cent glycerin and 33 per cent of a physiologic solution of sodium chloride containing 0.0908 per cent monopotassium phosphate and 0.238 per cent monosodium phosphate. The pollen is extracted for twenty two hours in a ball mill, pulped and clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of dried pollen. Each cubic centimeter represents 30,000 pollen units, one pollen unit being the equivalent of 0.001 mg. of dried pollen. The marketed products represent approximate dilution of this stock solution and are preserved with 0.5 per cent of phenol.

## Rhus Extracts

*Rhus toxicodendron*, *Rhus diversiloba*, and *Rhus venenata* are commonly known as poison ivy, oak and sumach. The first two are so closely related they are often confused. The last is a more distinct species. Poison ivy is prevalent east of the Rocky Mountains, while poison oak prevails along the Pacific coast.

Contact dermatitis occurs in susceptible people. It is caused by resinaceous substance extractable from the leaves with alcohol, acetone, and other lipid solvents. The substances extracted from poison ivy and poison oak are closely related chemically and may be used interchangeably for the preseasonal immunization or the treatment of ivy or oak dermatitis. Sensitivity to sumach, according to some observers, is identical with that of ivy, and ivy extracts have been used for sumach prophylaxis.

According to some observers immunity may be established by the oral administration of highly diluted alcoholic extracts given in gradually increasing doses, or by repeated intramuscular injections. The acute dermatitis has been treated by intramuscular injections. These injections are often followed by severe reactions and exacerbations of the dermatitis when caution is not used regarding the dosage. In general when injections of the extract are used for immunization or treatment, frequently given small doses are more satisfactory than a few large doses given at longer intervals.

**POISON IVY EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus toxicodendron*.

*Actions and Uses*—Poison ivy extract is used for prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus toxicodendron*.

*Dosage.*—In cases of average susceptibility 0.5 to 1.0 cc. may be given intramuscularly, repeated every 12 to 48 hours until relieved. In cases of unusual susceptibility injections of from 0.2 to 0.35 cc. are given, increased or not as indicated. For prophylaxis two injections of 10 cc. each may be given two weeks apart.

## ABBOTT LABORATORIES

**Poison Ivy Extract:** Packages of two 1 cc ampoules. Each cubic centimeter contains 45 mg of desiccated oily resin in a mixture of sweet almond and peanut oils.

Fresh leaves of *Rhus toxicodendron* are extracted with methanol. The solvent is removed in vacuo. The residue is dissolved in isopentane and decolorized by agitation with magnesium trisilicate. The solvent is removed in vacuo, and the residue is dissolved in a sterile mixture of sweet almond and peanut oils containing chlorobutanol, so that the finished solution contains 45 mg of the residue per cubic centimeter and 0.5 per cent W/V chlorobutanol.

## HOLLISTER-STIER LABORATORIES

**Poison Ivy Extract:** Packages of five ampuls, each containing 0.2 cc of alcoholic extract, with five ampuls of sterile salt solution for dilution immediately before administration.

Ten Gm of mature leaves of *Rhus toxicodendron* are dried, pulverized and extracted seventy-two hours in 100 cc of absolute ethyl alcohol. The extract is decolorized and sterilized by filtration.

## MULFORD COLLOID LABORATORIES

**Ampul-Vials Rhus Tox. Antigen** 1 cc. Each cc contains 75 mg of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus toxicodendron* are extracted with ethyl alcohol, the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll, and then treated with zinc sulfate, sodium phosphate is then added to precipitate the zinc as zinc phosphate, the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isopropyl alcohol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.

## PARKE, DAVIS &amp; COMPANY

**Poison Ivy Extract:** Packages of six 1 cc ampuls. A 15 per cent solution of poison ivy extract *Rhus toxicodendron* (poison ivy—poison oak) antigen in almond oil.

The dried leaves of poison ivy (*Rhus toxicodendron*) are extracted with toluene. The resulting extract is dehydrated and decolorized and then concentrated to a solid. The residue is dissolved in sterile almond oil containing 0.5 per cent chlorethone as a preservative. Sufficient oil is used to make a 15 per cent extract.

## PITMAN-MOORE COMPANY

**Poison Ivy Extract with Sterile Diluent:** 1 cc vial marketed in a package also containing three 0.9 cc vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Fresh leaves of *Rhus toxicodendron* dried at temperatures not exceeding 60 C and sieved to remove stems and leaf midribs, are macerated with absolute ethyl alcohol using 20 cc of alcohol for each gram of dried leaves. The extract is filtered through paper, then diluted to five times its original volume by adding absolute ethyl alcohol.

The following product is supplied in 5 cc. vials representing 30,000 pollen units per cubic centimeter:

*Grasses Combined (Bermuda, June Grass, Orchard Grass, Red Top, Sweet Vernal Grass and Timothy in equal parts).*

Prepared by extracting the dried pollen with a menstruum containing 67 per cent glycerin and 33 per cent of a physiologic solution of sodium chloride containing 0.0203 per cent monopotassium phosphate and 0.238 per cent monosodium phosphate. The pollen is extracted for twenty-two hours in a ball mill, pulped and clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of dried pollen. Each cubic centimeter represents 30,000 pollen units, one pollen unit being the equivalent of 0.001 mg. of dried pollen. The marketed products represent approximate dilution of this stock solution and are preserved with 0.5 per cent of phenol.

### Rhus Extracts

*Rhus toxicodendron*, *Rhus diversiloba*, and *Rhus venenata* are commonly known as poison ivy, oak and sumach. The first two are so closely related they are often confused. The last is a more distinct species. Poison ivy is prevalent east of the Rocky Mountains, while poison oak prevails along the Pacific coast.

Contact dermatitis occurs in susceptible people. It is caused by resinaceous substance extractable from the leaves with alcohol, acetone, and other lipid solvents. The substances extracted from poison ivy and poison oak are closely related chemically and may be used interchangeably for the preseasonal immunization or the treatment of ivy or oak dermatitis. Sensitivity to sumach, according to some observers, is identical with that of ivy, and ivy extracts have been used for sumach prophylaxis.

According to some observers immunity may be established by highly diluted alcoholic extracts, or by repeated intramuscular injections. Dermatitis has been treated by injections are often followed by severe reactions and exacerbations of the dermatitis when caution is not used regarding the dosage. In general when injections of the extract are used for immunization or treatment, frequently given small doses are more satisfactory than a few large doses given at longer intervals.

**POISON IVY EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus toxicodendron*.

**Actions and Uses.**—Poison ivy extract is used for prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus toxicodendron*.

**Dosage.**—In cases of average susceptibility 0.5 to 1.0 cc. may be given intramuscularly, repeated every 12 to 48 hours until relieved. In cases of unusual susceptibility injections of from 0.2 to 0.35 cc are given, increased or not as indicated. For prophylaxis two injections of 10 cc each may be given two weeks apart.

## ABBOTT LABORATORIES

**Poison Ivy Extract.** Packages of two 1 cc ampoules. Each cubic centimeter contains 45 mg of desiccated oily resin in a mixture of sweet almond and peanut oils.

Fresh leaves of *Rhus toxicodendron* are extracted with methanol. The solvent is removed in vacuo. The residue is dissolved in isopentane and decolorized by agitation with magnesium trisilicate. The solvent is removed in vacuo and the residue is dissolved in a sterile mixture of sweet almond and peanut oils containing chlorobutanol so that the finished solution contains 45 mg of the residue per cubic centimeter and 0.5 per cent W/V chlorobutanol.

## HOLLISTER STEER LABORATORIES

**Poison Ivy Extract:** Packages of five ampuls, each containing 0.2 cc of alcoholic extract, with five ampuls of sterile salt solution for dilution immediately before administration.

Ten Gm of mature leaves of *Rhus toxicodendron* are dried, pulverized and extracted seventy-two hours in 100 cc of absolute ethyl alcohol. The extract is decolorized and sterilized by filtration.

## MULFORD COLLOID LABORATORIES

**Ampul-Vials Rhus Tox Antigen.** 1 cc. Each cc contains 75 mg of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus toxicodendron* are extracted with ethyl alcohol; the alcohol is removed; the residue is extracted with chloroform to remove the chlorophyll and then treated with zinc sulfate, sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isopropyl alcohol. In an extraction apparatus, the extractions are evaporated and the residual extract dried at a low temperature.

## PARK, DAVIS &amp; COMPANY

**Poison Ivy Extract.** Packages of six 1 cc ampuls. A 15 per cent solution of poison ivy extract *Rhus toxicodendron* (poison ivy—poison oak) antigen in almond oil.

The dried leaves of poison ivy (*Rhus toxicodendron*) are extracted with toluene. The resulting extract is dehydrated and decolorized and then concentrated to a solid. The residue is dissolved in sterile almond oil containing 0.5 per cent chloroform as a preservative. Sufficient oil is used to make a 15 per cent extract.

## FITZMAN-MOORE COMPANY

**Poison Ivy Extract with Sterile Diluent.** 1 cc vial marketed in a package also containing three 0.9 cc vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Fresh leaves of *Rhus toxicodendron* dried at temperatures not exceeding 60 C and severed to remove stems and leaf petioles are macerated with absolute ethyl alcohol using 20 cc of alcohol for each gram of dried leaves. The extract is filtered through paper then diluted to five times its original volume by adding absolute ethyl alcohol.



## SHARP &amp; DOHME, INC.

**'Ivyol' Poison Ivy Extract:** A 1:1,000 solution in olive oil with 2 per cent camphor as a preservative.

U. S. Patent 1,559,340 (October 27, 1925, expires 1942). U. S. Trademark 229,039.

The fresh leaves of *Rhus toxicodendron* are extracted with purified petroleum benzin. The resulting extract is filtered through paper and decolorized by agitation with fuller's earth. The decolorized extract is concentrated in vacuo to one tenth its original volume; the concentrated extract is allowed to evaporate spontaneously to dryness; and the residue dissolved in sterile olive oil.

**POISON OAK EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus diversiloba*.

**Actions and Uses.**—Poison oak extract is used for the prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus diversiloba*.

**Dosage.**—In cases of average susceptibility 0.7 to 1.0 cc. may be injected intramuscularly at intervals of 24 to 48 hours. In cases of unusual susceptibility, smaller doses should be employed, increased or not as indicated. For prophylaxis two injections of 1 cc. each may be made, separated by an interval of two weeks.

## HOLLISTER-STIER LABORATORIES

**Poison Oak Extract:** Packages of five ampuls, each containing 0.2 cc. of alcoholic extract, with five ampuls of sterile salt solution for dilution immediately before administration.

Ten Gm. of mature leaves of *Rhus diversiloba* are dried, pulverized and extracted seventy-two hours in 100 cc. of absolute ethyl alcohol. The extract is decolorized and sterilized by filtration.

## PITMAN-MOORE COMPANY

**Poison Oak Extract with Sterile Diluent:** 1 cc. vial, marketed in a package also containing three 0.9 cc. vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Fresh leaves of *Rhus diversiloba*, dried at temperatures not exceeding 60 C. and sieved to remove stems and leaf midribs, are macerated with absolute ethyl alcohol, using 20 cc. of alcohol for each gram of dried leaves. The extract is filtered through paper, then diluted to five times its original volume by adding absolute ethyl alcohol.

**POISON SUMACH EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus venenata*.

**Actions and Uses.**—Poison sumach extract is used for the prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus venenata*.

**Dosage.**—In cases of average susceptibility initial intramuscular injections of 0.5 to 1.0 cc. may be given. In cases of unusual susceptibility smaller doses should be employed, increased or not as indicated. When indicated, subsequent injections of

10 cc may be given every 12 to 24 hours until the dermatitis is controlled. For prophylaxis two injections of 1 cc each may be given, separated by an interval of two weeks.

#### MULFORD COLLOID LABORATORIES

**Ampul-Vials Rhus Venenata Antigen** 1 cc Each cc contains 75 mg of substance dissolved in 35 per cent alcohol

Freshly gathered leaves of *Rhus venenata* are extracted with ethyl alcohol the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll and then treated with zinc sulfate, sodium phosphate is then added to precipitate the zinc as zinc phosphate, the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isobutyl alcohol in an extraction apparatus the extractions evaporated and the residual extract dried at a low temperature.

## CHAPTER II

### ANALGESICS AND ANTIPYRETICS

#### Cinchophen and Derivatives

Cinchophen was introduced in therapeutics under the proprietary name "atophan." It was admitted to the U. S. Pharmacopeia IX as *acidum phenylcinchoninicum*, the name being later changed to *cinchophennum*. It was omitted from the U. S. P. XI and is now official in the N. F. VII. Cinchophen and its compounds are derived from quinoline carboxylic acid. Cinchophen is 2-phenyl-4-carboxyquinoline. Neocinchophen (introduced as novatophan) is 2-phenyl-4-carbethoxy-6-methylquinoline. Cinchophen has a slightly bitter taste, while neocinchophen is practically tasteless, otherwise their actions are closely similar.

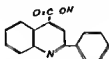
Cinchophen and cinchophen derivatives increase the permeability of the kidneys selectively to uric acid, and therefore greatly increase the excretion of the urates in the urine. Under a purin-free diet the amount of uric acid in the blood is reduced one-half; when exogenous purins are given, the total amount is rapidly excreted so that the content of uric acid in the blood remains at normal or below. The influence of the cinchophen on uric acid excretion is greater and is exerted more promptly than that of sodium salicylate. Its action grows weaker after the first three hours and is practically terminated in nine hours after the administration of the dose. The amount of ammonia and that of total nitrogen in the urine are slightly increased during the action of cinchophen, but not in proportion to the increase in the uric acid of the urine. Cinchophen does not increase the leukocytes, the purin bases or the phosphoric acid. There is no evidence of increased formation of uric acid or of any effect on deposited urates.

While the ordinary doses of cinchophen are usually harmless they are occasionally followed by severe and even fatal effects. These are more frequent with the larger doses. Symptoms of acute intoxication include a sense of oppression in the gastric region with acid eructation and diarrhea, which in some cases can be avoided by the simultaneous use of small doses of sodium bicarbonate. In cystitis it may cause pain in the bladder with hematuria. It occasionally induces a scarlet, an urticaria-like, or a vesiculous rash. It sometimes induces cardiac distress with dizziness. Excessive doses or the long continued use of moderate amounts may cause damage to the kidney and occasionally gives rise to acute yellow atrophy or to dangerous or fatal hepatitis, usually characterized by the late and relatively abrupt onset of symptoms, the most frequent being jaundice. The appearance of skin rash, vomiting, anorexia, albuminuria, heartburn, diarrhea or jaundice requires the immediate discontinuance of the drug. Relatively small doses occasionally induce symptoms in patients showing idiosyncrasy, and it is possible

that an attack of hepatitis renders the patient extremely susceptible to further medication at a later date. Especial caution is necessary in the use of cinchophen in the presence of renal insufficiency. The promiscuous use of cinchophen by the public for the relief of pain is obviously dangerous. Fewer cases of poisoning have been reported after neocinchophen, but the relative danger of these two has not been determined satisfactorily. There is perhaps some reason to believe that neocinchophen is less likely to prove toxic, but the evidence is not conclusive. The same contraindications and precautions should be observed in the use of neocinchophen as in the case of cinchophen.

Avoidance of the contraindications, special attention to the diet, and effective supervision of the patient are important, but it should not be felt that they render the drug safe. As a supplement to a Council report (J A M A 117:1182 [Oct 4] 1941) on the present status of cinchophen and neocinchophen there was made available a tabulation of the replies to a questionnaire on cinchophen and cinchophen derivatives sent by the Food and Drug Administration. This tabulation revealed that 82 per cent of those questioned feel that these agents are not indispensable in the physician's armamentarium, 71 per cent are of the opinion that cinchophen and cinchophen derivatives do not have any essential therapeutic effect which cannot be accomplished by properly regulated doses of other medicaments, 79 per cent assert that the preparations cannot be administered in therapeutically active doses with confidence that serious deleterious effects will not supervene, and 77 per cent are of the opinion that the pathology of cinchophen poisoning cannot be counteracted or cured by specific measures once the symptoms of poisoning have appeared.

**CINCHOPHEN** — Phenylcinchonine Acid — Phenylquinolinecarboxylic Acid —  $N$  F — 2 phenyl 4 carboxyquinoline — Contains when dried to constant weight at  $100^{\circ} \text{C}$ , not less than 99.5 per cent of  $\text{C}_{15}\text{H}_{11}\text{N} \cdot \text{C}_6\text{H}_5\text{COOH}$  2:4'  $N$  F



For description and standards see The National Formulary under Cinchophenum and Tabellae Cinchopheni.

**Actions and Uses**—Cinchophen is useful in acute gout, it relieves pain in this disease, acting more promptly than colchicum and, when proper dosage is used, generally without undesirable by effects. In nonuratic joint affections, particularly acute articular rheumatism favorable results are reported while the chronic forms seem to yield to cinchophen only in isolated cases. It frequently relieves the pain of sciatica, but not invari-

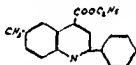
ably according to McLester (*Arch. Int. Med.* 12:739 [Dec.] 1917). It is not known whether it is effective in the treatment of malaria.

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poor in carbohydrates and the onset of any of the symptoms of cinchophen poisoning. The drug should not be employed unless the attending physician feels that the patient's need for it fully justifies the risk, possibly for the relief of pain in certain cases of so-called rheumatism, including gout, and some types of arthritis when safer substitutes fail to afford relief.

**Dosage.**—In gout the dose of cinchophen is from 0.5 Gm. four times a day to 1 Gm. three times a day suspended in large quantities of water. In order to prevent the precipitation of free uric acid from the urine with possibly resulting renal colic, Weintraub considers it necessary to administer simultaneously 15 Gm. of sodium bicarbonate in the course of the first day and from 5 to 10 Gm. on the following days. In articular rheumatism, Heller prescribed daily doses of from 3 to 5 Gm.

**NEOCINCHOPHEN.**—*l'* S. *P'*—The ethyl ester of 6-methyl-2-phenylquinoline-4-carboxylic acid



For description and standards see the U. S. Pharmacopeia under Neocinchophen and Tabellae Neocinchopheni

**Actions and Uses.**—The same as those of cinchophen

**Dosage.**—0.3 Gm. See dosage statement for Cinchophen

### Para-Aminophenol Derivatives



The members of this group (sometimes known as the phenetidins) are derivatives of para-aminophenol ( $C_6H_4(NH_2)(OH)$ , 1,4) and are chemically related to aniline (aminobenzene). The derivatives have similar pharmacologic properties, and as they undergo decomposition in the tissues to yield either para-aminophenol or acetaminophenol, any difference in activity may be largely due to the rapidity with which this decomposition occurs.

antipyretics and anal-  
 -se effects. However,  
 effects and should be  
 d may vary not only  
 with the dose but with the individual patient. Undesirable  
 reactions which have been reported following the use of anti-  
 pyretics include skin eruptions, catarrh, edema of the throat  
 and mouth, nausea and vomiting, disturbances of hearing, con-  
 fusion, blood changes, heart depression and circulatory collapse.  
 The employment of such drugs in infectious fevers should be  
 most cautious.

Nearly every newly discovered product related to acetophe-  
 netidin has been heralded as a "safe" antipyretic and free from  
 poisonous effects on the blood and heart. Invariably, extended  
 clinical experience has shown that all of these preparations  
 have, to a greater or less degree, an effect on the blood and  
 circulation.

**PHENETSAL** — Phenetsalum — Salophen — Acetyl *p*  
 aminophenyl Salicylate — Acet *p* aminosalol — 1,4 Acetamino  
 phenyl Salicylate —  $C_6H_4(OH)COOC_6H_4(NHCH_3CO)$  The  
 salicylic acid ester of 1,4 acetaminophenol,  $C_6H_4(NHCH_3CO)$   
 (OH)

**Actions and Uses**—The actions of phenetsal resemble those  
 of phenyl salicylate (salol). It is not changed in the stomach  
 but is broken up in the intestine, liberating salicylic acid and  
 para aminophenol (which is less toxic than phenol). It acts as  
 an antirheumatic, antipyretic and analgesic. It is said to be  
 useful in rheumatism, gout and typhoid fever. Externally, it has  
 been applied in psoriasis and itching skin diseases.

**Dosage**—From 0.3 to 1 Gm., in powder wafers or capsules.  
 Externally, in 10 per cent ointment.

#### **Tests and Standards**—

Phenetsal forms small white crystalline leaflets or powder, odorless  
 and tasteless, melting at from 137 to 138 C. It is almost insoluble  
 in cold water, more soluble in warm water, freely soluble in watery  
 solutions of the alkalis and in alcohol, ether and benzene, but not in  
 petroleum benzine.

If its alkaline solution is boiled it gradually becomes blue, on con-  
 tinuing the boiling the color is discharged, but is again produced on  
 cooling and exposure to air. On the addition of ferric chloride to the  
 alkaline solution the violet color characteristic of salicylic acid is  
 produced, but a simple aqueous solution of phenetsal does not react  
 with ferric chloride and should not be changed by silver nitrate.  
 It forms a colorless solution with concentrated sulfuric acid.

It is incompatible with alkalis which decompose it.

**WINTHROP CHEMICAL COMPANY, INC.**

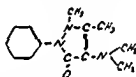
Salophen (Powder) • bulk Phenetsal — N N R  
 Tablets Salophen 0.325 Gm.

U. S. Trademark 20 759

## Pyrazolon Derivatives

The preparations in this group are used for their antipyretic and analgesic action and in general are subject to the same caution statements that govern the use of the phenetidin compounds. On taking small doses, some susceptible individuals experience nervous and circulatory depression, while after large doses instances of collapse have been reported. In the treatment of infectious fevers, they, as other antipyretics, should be cautiously employed. (See the general section, Para-aminophenol Derivatives.) Serious and sometimes fatal granulocytopenia may appear, especially in susceptible individuals. The drug should be immediately withdrawn if a skin eruption, dizziness, throat irritation or chill occurs; it should not be administered in large doses or over a long period of time unless repeated leukocyte and differential blood counts are made at frequent intervals. The slightest untoward symptoms are indications for withdrawal of the drug and immediate leukocyte differential count.

**AMINOPYRINE.**—Amidopyrine.—U. S. P.—Dimethylaminophenyldimethylpyrazolon.—Pyramidon.



For description and standards see the U. S. Pharmacopeia under Aminopyrina and the National Formulary under Elixir Aminopyrinae and Tabellae Aminopyrinae.

*Actions.*—As a Pyrazolon Derivative, it acts as an antipyretic and analgesic. It is used in small doses for the relief of pain and fever, and in larger doses for the relief of dysmenorrhea or for any other purpose at or near the menstrual period. Special attention is called to the dangerous side actions mentioned in the preceding article, Pyrazolon Derivatives.

*Dosage.*—From 0.3 to 0.4 Gm., most conveniently in the form of tablets, a single dose usually sufficing for twenty-four hours.

**ABBOTT LABORATORIES**

Tablets Aminopyrine: 0.325 Gm.

**MERCK & CO., INC.**

Aminopyrine (*Powder*): bulk.

THE WM S MERRELL CO.

Tablets Aminopyrine: 0.324 Gm

WINTHROP CHEMICAL COMPANY, INC

Pyramidon (Powder) - bulk

Elixir of Pyramidon: Each 4 cc contains pyramidon, 0.162 Gm in a menstruum containing alcohol 20 per cent

Tablets Pyramidon: 0.13 Gm and 0.325 Gm

U S patent expired U S Trademark

## Salicylic Acid Compounds



To avoid the disagreeable taste and gastric symptoms of salicylic acid and its salts, esters of salicylic acid have been introduced, which are more or less insoluble, so that the salicyl radical is liberated only in the intestine or after absorption into the blood. These compounds may exert direct action on the stomach, recent work suggests the possibility of gastric ulcer formation if the compounds are not properly diluted or made other-  
 In this respect, these salicylate, which does properly guarded by less objectionable

Compounds which hydrolyze to produce salicylic acid may be of the following types

- 1 Simple salts of salicylic acid, e g, sodium salicylate
- 2 Acyl esters of salicylic acid involving the phenolic hydroxyl group, e g acetylsalicylic acid
- 3 Alkyl and aryl esters of salicylic acid involving the carboxylic group e g methyl salicylate and phenyl salicylate respectively

The acyl derivatives (acetylsalicylic acid type) possess a higher analgesic and antipyretic action than simple salicylate salts

The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates

The aryl esters (phenyl salicylate type) hydrolyze to active phenols and salicylic acid. They have been used for intestinal antiseptics but are of doubtful value



**EQUIVALENTS OF 100 PARTS OF VARIOUS SALICYLIC ACID DERIVATIVES IN TERMS OF SALICYLIC ACID AND SODIUM SALICYLATE:**

100 Parts of	Equivalent Parts of Salicylic Acid	Equivalent Parts of Sodium Salicylate
Salysal .....	106.2	124
Salicylic acid .....	100	116
Sodium salicylate ....	86	100
Acetylsalicylic acid .....	77	89
Sal-Ethyl carbonate .....	77	89
Novaspirin ..	62	72

***Acid Derivatives (Acyl Esters) of Salicylic Acid***

These are employed as analgesics and antipyretics in rheumatic conditions, and in colds, neuralgias, etc. Their analgesic effects surpass those of sodium salicylate. Their acid character causes some local irritation, which may be quite marked when large doses are taken. The promiscuous use of acetylsalicylic acid (aspirin) by the laity, especially for the relief of headache, has led to rather severe poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose or of the entire face; also urticarial rashes, vertigo, nausea and sometimes cyanosis. Atopic asthmatic persons are especially susceptible to these effects of acetylsalicylic acid and several deaths have been reported from its use by such individuals.

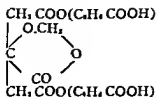
**ACETYLSALICYLIC ACID.**—Aspirin — "When dried over sulfuric acid for 5 hours, contains not less than 99.5 per cent of  $\text{HC}_7\text{H}_5\text{O}_2 \cdot \text{C}_2\text{H}_3\text{O}_2$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Acidum Acetylsalicylicum*.

**Actions and Uses.**—See preceding article, Acid Derivatives (Acyl Esters) of Salicylic Acid.

**Dosage.**—From 0.3 to 1 Gm., repeated once in three hours until symptoms of salicylism (ringing in the ears, etc) are noted. It may be administered in the form of powder; this may be administered by placing it on the tongue and taking a swallow of water. The powder should be dispensed in wax paper.

**NOVASPIRIN.** — Salicitrin. — Methylene-Citrylsalicylic Acid,



(F

*Dosage*—1 Gm, several times daily*Tests and Standards*—

Novaspirin is a grayish white odorless crystalline powder stable in the air having a faint acidulous taste. It is almost insoluble in water, soluble in alcohol, less soluble in ether or chloroform. On heating novaspirin with caustic alkalis salicylate is formed and on adding diluted acid to the alkaline solution crystals of salicylic acid are separated. On long standing in the presence of water or more quickly with alkalis novaspirin is split into its components. When heated in a dry test tube novaspirin melts and at higher temperatures formaldehyde and salicylic acid are liberated. The salicylic acid sublimes and is deposited on the cooler portions of the tube. Novaspirin when decomposed yields 62 per cent of salicylic acid. After drying over sulfuric acid to constant weight novaspirin melts at from 153 to 154 C. A saturated aqueous solution of novaspirin (prepared without heat) does not produce a violet color with ferric chloride solution.

Incinerate 1 Gm of novaspirin not more than 0.1 per cent of ash remains.

Dry 1 Gm. of novaspirin over sulfuric acid the loss in weight is not more than 5 per cent.

WINTHROP CHEMICAL COMPANY, INC

Novaspirin (Powder) bulk

Tablets Novaspirin 0.325 Gm

U. S. Patent 858 142 (June 25 1907, expired) U. S. Trade Mark 62 613

**SALYSAL**—The salicylic ester of salicylic acid— $\text{HO C}_6\text{H}_4\text{COO C}_6\text{H}_4\text{COOH}$

*Actions and Uses*—See preceding article, Acid Derivatives of Salicylic Acid. Being insoluble in water and dilute acids salysal is said to be relatively free from disagreeable taste and local irritating action.

*Dosage*—From 0.3 to 0.6 Gm two to three times a day. Salysal is approximately twice as active therapeutically as sodium salicylate and may be employed in one half the dosage of the latter drug.

*Tests and Standards*—

Salysal occurs as a white odorless tasteless stable crystalline powder. It is soluble in alcohol, ether and solutions of alkalis, slightly soluble in benzene and insoluble in water and dilute acids. Salysal melts at 147 to 149 C.

Dissolve 0.5 Gm of salysal in 5 cc of sulfuric acid, no more than a faint yellow color appears (*readily carbonizable substance*). Shake 1 Gm of salysal with 25 cc. of cold water, filter and add 1 cc. of ferric chloride solution, no violet color appears (*free salicylic acid*). Dissolve  $\frac{1}{2}$  Gm. of salysal in 10 cc of alcohol and add 1 cc. of dilute nitric acid and 1 cc. of silver nitrate solution, no precipitate is produced (*chlorides*). Incinerate about 2 Gm of salysal accurately weighed, the ash does not exceed 0.25 per cent. Dry about 1 Gm of salysal accurately weighed to constant weight at 103 C, the loss in weight does not exceed 0.5 per cent.

Transfer about 0.5 Gm. of salysal, previously dried and accurately weighed to a 200 cc. flask and add 50 cc. of diluted alcohol which has

## RARE CHEMICALS, INC.

Salysal (*Powder*): bulk

Tablets Salysal: 0.325 Gm.

U. S. Patent 922,995 (May 25, 1909; expired). The firm has relinquished Trademark rights to the name

## *Alkyl Esters of Salicylic Acid*

These act somewhat more slowly, but otherwise as efficiently as sodium salicylate. They are for the most part saponified in the intestines, but some may be absorbed unchanged. They frequently cause somewhat more local irritation. They are also quite well absorbed from the skin, and may, therefore, be applied externally, usually dissolved in olive oil. Methyl salicylate is official in the U. S. Pharmacopeia

**ETHYL SALICYLATE.**—Aethylis Salicylas.— $C_6H_5OH.CO.O(C_2H_5)$ .—The salicylic acid ester of ethyl alcohol analogous to methyl salicylate (oil of wintergreen).

*Actions and Uses.*—Ethyl salicylate has the same action as methyl salicylate, but is said to be less irritant and less toxic

*Dosage.*—From 0.3 to 0.6 cc. three or four times a day

### *Tests and Standards*—

Ethyl Salicylate is a transparent, colorless, volatile liquid, possessing a pleasant characteristic odor and taste. Its specific gravity is 1.132 at 20 C. and it boils at from 230 to 232 C. It is insoluble in water, but soluble in alcohol

## PARKE, DAVIS & COMPANY

Capsules Sal-Ethyl: 0.3 cc

U. S. Trademark 92,115

**MESOTAN.**—Salmester.— $C_6H_5OH.CO.O(CH_2OCH_3)$ —Methoxymethyl salicylate, an ester of salicylic acid, analogous to methyl salicylate

*Actions and Uses.*—Mesotan is an active counterirritant, used especially in rheumatic conditions, similarly to the local application of methyl salicylate. It is more irritant than the latter, and lacks its odor. It is absorbed from the skin, but its action is predominantly local, relieving pain and swelling. It is not an efficient means for producing the systemic actions of salicylates

**Dosage**—Mesotan diluted with 1 to 4 parts of olive oil or cotton seed oil is painted over the affected area usually twice daily. Friction should not be used, and dressings, if any are necessary, should be light and permeable. The site of application should be changed, if possible, after each treatment; or the area may be rested for two days after four days of treatment.

#### *Tests and Standards—*

Mesotan is a clear yellowish, faintly aromatic, oily fluid specific gravity 1.2 at 15 C. and boiling at about 162 C. It is but slightly soluble in water, but readily soluble in the usual organic solvents and miscible with oils in all proportions. About 100 C it is decomposed, yielding salicylic acid, formaldehyde and methyl alcohol, and it is likewise decomposed to a certain extent by moisture in the air.

The aqueous solution of mesotan gives a violet color with ferric chloride and, after heating or exposure to moisture it responds to the usual tests for formaldehyde. Concentrated sulfuric acid colors it red.

Mesotan should be kept in a cool place and preserved dry in well stoppered bottles.

#### WINTHROP CHEMICAL COMPANY, INC

Mesotan (Liquid) bulk

U S Patent 706 018 (Aug 5 1902 expired) U S Trademark 39 017

**SAL-ETHYL CARBONATE**—The carbonic acid ester of ethyl salicylate—Salicylic ethyl ester carbonate— $\text{O C}(\text{OCH}_2\text{CH}_3)_2\text{COOC}_2\text{H}_5$ .

**Actions and Uses**—Sal ethyl carbonate provides the antipyretic and analgesic effects of the salicylates. It is relatively insoluble in water and in the acid secretions of the stomach practically avoiding the disagreeable taste and local gastric symptoms of the soluble salicylates. For cases requiring a rapid analgesic and antipyretic effect rather than salicylate saturation, tablets sal ethyl carbonate with aminopyrine are supplied, but it should be recalled that aminopyrine may produce dangerous granulocytopenia in occasional individuals.

**Dosage**—Sal ethyl carbonate and tablets sal ethyl carbonate with aminopyrine may be given in dosages ranging from 0.3 to 1 Gm three or four times daily, according to the individual requirements.

#### *Tests and Standards—*

Sal ethyl carbonate occurs as white odorless and tasteless crystals. It is almost insoluble in water and diluted hydrochloric acid. It is slightly soluble in ether and alcohol but readily soluble in chloroform and acetone. It melts between 96 and 99 C.

**Transfer about 2 Gm of sal ethyl carbonate to a test tube add 5 cc of half normal alcoholic potassium hydroxide and heat on the steam bath for five minutes the product dissolves and the formation of a precipitate follows cool decant the supernatant liquid add 5 per cent acetic acid to the precipitate it effervesces add an equal volume of water to the decanted liquid a colorless oil separates having the odor**

of ethyl salicylate. Transfer about 1 Gm. of sal-ethyl carbonate to an Erlenmeyer flask, add 20 cc. of alcohol and boil under a reflux condenser the solution by addition of dilute with 20 cc. of ether, filter the responds to qualitative tests for salicylic acid.

Dissolve about 0.5 Gm. of sal-ethyl carbonate in 10 cc. of sulfuric acid: the solution remains colorless for five minutes (*readily carbonizable substances*). Transfer about 0.5 Gm. of sal-ethyl carbonate to a test tube, add 10 cc. of water and a few drops of ferric chloride solution: no blue color develops (*salicylic acid*).

Transfer about 1 Gm. of sal-ethyl carbonate, accurately weighed, to an Erlenmeyer flask, add 40 cc. of half normal alcoholic potassium hydroxide, boil under a reflux condenser on the steam bath for three hours, wash the condenser and add the washings to the flask, remove the alcohol by evaporating to about one-third the volume, adding 50 cc. of water and evaporating to about 15 cc., transfer the solution to a 250 cc. volumetric flask, make up to volume by addition of water. Transfer a 25 cc. aliquot to an Erlenmeyer flask and test the solution according to the method for total salicylate described in the A. O. A. C. Manual, third edition, page 446, Iodine Method, paragraph 24; the weight of the tetraiodophenylene quinone multiplied by 0.5208 and by the aliquot factor is equivalent to not less than 98.5 per cent nor more than 100.5 per cent of the sample taken. Transfer about 1 Gm. of sal-ethyl carbonate, accurately weighed, to a tared weighing bottle; heat in an oven at 100 C. for one hour; cool in a desiccator and weigh; the loss in weight is not greater than 1 per cent. Transfer about 0.5 Gm. of sal-ethyl carbonate, accurately weighed, to a platinum dish and ignite; the ash is not more than 0.2 per cent.

## PARKE, DAVIS & COMPANY

Sal-Ethyl Carbonate (*Powder*): bulk.

Tablets Sal-Ethyl Carbonate: 0.325 Gm.

Tablets Sal-Ethyl Carbonate with Aminopyrine: Each tablet contains sal-ethyl carbonate 0.23 Gm. and aminopyrine U. S. P 01 Gm.

U. S. Trademark 92,115.

**SPIROSAL.**—Monoglycol-Salicylate.—Glysal.— $C_6H_4(OH)CO.O.(CH_2CH_2OH)$ .—The salicylic acid ester of monoglycol.

*Actions and Uses.*—See preceding article, Alkyl Esters of Salicylic Acid. When spirosal is applied to the skin from about one-fifth to one-sixth of the amount used is absorbed. Usually it causes very little irritation even when rubbed in thoroughly.

*Dosage.*—It is used undiluted or mixed with from 2 to 3 parts of alcohol or in a mixture with olive oil, 1 to 8, or in ointments with equal parts by weight of petrolatum or lard.

### Tests and Standards.—

Spirosal is an almost odorless and colorless oily fluid, with a boiling-point of from 169 to 170 C. at 12 mm. pressure. It is easily soluble in alcohol, ether, chloroform and benzol and soluble in about 110 parts of water and 8 parts of olive oil.

When 0.5 Gm spirosal is saponified with 5 cc sodium hydroxide solution by slight warming, the clear fluid diluted with water and acidified with dilute sulfuric acid, fine crystalline needles of salicylic acid are formed which after being extracted with ether and the latter then evaporated can be identified by the melting point and ferric chloride reaction. The saturated aqueous solution obtained by shaking 1 cc of spirosal with 50 cc. of water gives a filtrate, which becomes intensely violet on addition of ferric chloride, but should not be changed by barium nitrate or silver nitrate solution. Five tenths Gm of spirosal when added to 2 cc of concentrated sulfuric acid should give a light yellow and not a brownish color. 0.3 Gm, if incinerated on platinum foil, should not leave any weighable residue.

**WINTHROP CHEMICAL COMPANY, INC**

**Spirosal (Liquid): bulk**

U S Patent 794 982 (July 18 1905, expired) U S Trademark  
62 856

## CHAPTER III ANESTHETICS

### Local Anesthetics

There are three general groups of drugs used for the production of local anesthesia: (1) those which cause anesthesia through the production of cold, such as ether, ethyl chloride and methyl chloride; (2) certain protoplasmic poisons, as quinine, and (3) those having a specific effect on sensory nerves or their endings, cocaine being the type of this class.

The drugs listed below belong, in general, to the third class. They have been introduced with the object of finding substances less toxic and more stable and less injurious to the tissues than cocaine. Their anesthetic power is also as a rule somewhat less than that of cocaine and some of them present the usually undesirable effect of dilating the blood vessels or at least of not constricting them as does cocaine, and are therefore almost always employed in conjunction with epinephrine. The most important are based on the discovery that the local anesthetic action of cocaine is due to the radical of benzoic acid in combination with a nitrogen-containing basic group. The simplest of these compounds, ethylaminobenzoate (benzo-

para-aminobenzoic acid,  
ethyl ester of hydroxy-

These are too weak  
useful for hypodermic  
injection; they are used for local application (See Slightly Soluble Local Anesthetics). Procaine hydrochloride is the hydrochloride of a compound of para-aminobenzoic acid with diethyl-aminoethyl alcohol; its salts are readily soluble in water. Only those local anesthetics of relatively low toxicity should be injected or others where very small amounts are required.

The local anesthetics can be used with safety in nearly all suitable cases if precautions are observed; but extreme caution is imperative when any local anesthetic is injected into the traumatized urethra or under conditions in which trauma is likely to occur. The details of dosage of any of the several local anesthetics should be learned with reference to various modifications for different applications.

### *Soluble Local Anesthetics*

**ALYPIN HYDROCHLORIDE.**—Amydricaine Hydrochloride.—The hydrochloride of 2-benzoxo-2-dimethylaminomethyl-1-dimethylaminobutane.

**Actions and Uses.**—Alypin hydrochloride is a local anesthetic, claimed to be equal to cocaine, but is not a mydriatic. It is said not to produce disturbance of accommodation and to be less toxic than cocaine, but the evidence as to the relative toxicity of alypin hydrochloride and cocaine is rather conflicting.





**AMYLCAINE HYDROCHLORIDE** (ämyl-cäine).—Mono-*n*-amyl-aminoethyl-*p*-aminobenzoate hydrochloride.— $\text{NH}_2\text{C}_6\text{H}_4\text{COO.CH}_2\text{CH}_2\text{NH.CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{HCl}$ .

**Actions and Uses.**—The actions of amylcaine hydrochloride resemble those of cocaine hydrochloride, but it does not cause mydriasis when the solution is dropped into the eye. In the present state of our knowledge its use should be restricted to the production of corneal anesthesia in those cases in which mydriasis is not desired. The toxicity varies rather widely with the species and with the mode of administration. The anesthesia is induced promptly with little smarting; it does not increase intraocular tension.

**Dosage.**—A 2 per cent solution is used in ophthalmology when mydriasis is not desired, 1 or 2 drops being usually sufficient.

**Tests and Standards.**—

.....

Dissolve 0.1 Gm. of amyleaine hydrochloride in 50 cc. of water, to one 5 cc. portion add 1 cc. of silver nitrate solution; a white precipitate results, soluble in excess of ammonia water; to another 5 cc. portion add 0.5 cc. of diluted hydrochloric acid, 0.5 cc. of a 10 per cent solution of sodium nitrite and then 10 cc. of ammonia water containing 0.2 Gm. of betanaphthol an orange precipitate results, soluble in ether; to a 2 cc. portion add 1 cc. of potassium mercuric iodide solution; a white precipitate results; to a 2 cc. portion add 2 cc. of picric acid solution; a yellow precipitate results. Dissolve 0.1 Gm. of amyleaine hydrochloride in 5 cc. of water, add 2 drops of sulfuric acid and 1 cc. of a saturated solution of sodium nitrite, and heat to 50 C.; a yellow oil separates (distinction from procaine, butyn, cocaine, tufocaine and pontocaine). Dissolve 0.1 Gm. of amyleaine hydrochloride in 1 cc. of sulfuric acid the solution is colorless (readily carbonizable substances). Saturate a solution of 0.1 Gm. in 10 cc. of water with hydrogen sulfide; no coloration or precipitation occurs (salts of heavy metals).

Transfer about 0.5 Gm. of amyleaine hydrochloride, accurately weighed, to a tared platinum dish and dry at 100 C. for six hours; the loss in weight does not exceed 3 per cent. Incinerate about 0.5 Gm. of amyleaine hydrochloride, accurately weighed; the ash does not exceed 0.1 per cent. Transfer a sample of amyleaine hydrochloride, previously dried and accurately weighed, to a Kjeldahl flask and digest with sulfuric acid in the presence of 0.1 Gm. of selenium; dilute, make alkaline with sodium hydroxide solution, distil into standard acid and titrate the excess acid with standard alkali; the nitrogen content is not greater than 9.8 nor less than 9.4 per cent. Transfer about 0.5 Gm. of amyleaine hydrochloride, previously dried and accurately weighed, to a 250 cc. beaker and dissolve in 100 cc. of water. Heat to boiling and add 10 cc. of nitric acid and 20 cc. of silver nitrate solution, digest on the steam bath for three hours, filter, wash, dry and weigh the precipitate; the chloride content is not greater than 12.5 nor less than 12.0 per cent.

## NOVOCOL CHEMICAL MFG Co., Inc

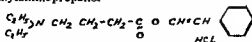
Amylcaine Hydrochloride (Powder) 5 Gm vials and 30 cc bottles

Amylcaine Hydrochloride Solution 2%, 120 cc bottles

Amylcaine Hydrochloride Solution 4%, 30 cc bottles

U S Patent 2 139 818 (Dec 13 1938 expires 1955) U S Trade mark 353 563

**APOTHESINE HYDROCHLORIDE**— $\gamma$  diethylamino propyl cinnamate hydrochloride The hydrochloride of a condensation product prepared by the action of cinnamoyl chloride on  $\gamma$  diethylaminopropanol



**Actions and Uses**—Apothesine hydrochloride is a local anesthetic of the procaine rather than the cocaine type that is it belongs to that type which while effective for injection anesthesia (especially when combined with epinephrine) is relatively inefficient when applied to mucous membranes. It is rather slower in action than procaine hydrochloride. Its absolute toxicity is about equal to that of cocaine but about twice that of procaine hydrochloride (as 20 is to 40). When injected somewhat stronger solutions are required than are necessary with procaine hydrochloride or especially with cocaine but with adequate concentrations the anesthesia is just as complete. It is employed for infiltration injection nerve blocking intraspinal injection pressure anesthesia and oral surgery as a palliative measure for its local anesthetic effect. Apothesine hydrochloride solutions are not injured by boiling. (See caution under the general article Local Anesthetics)

**Dosage**—As a local anesthetic 0.5 to 2 per cent solution generally with epinephrine hydrochloride in sterile water or physiologic solution of sodium chloride. For spinal anesthesia 2 cc of a 4 per cent solution.

### Tests and Standards—

Apothesine hydrochloride occurs in white masses which are composed of small white crystals practically odorless and faintly bitter but producing a sense of numbness of the tongue and stable in air. It is soluble in water and alcohol and slightly soluble in acetone or ether.

amnopropylalcohol and sodium cinnamate

Apothesine hydrochloride melts at 136 C.

An aqueous solution of apothesine hydrochloride gives with silver nitrate solution a white precipitate which is soluble in an excess of ammonia water.

Dissolve about 0.1 Gm. of apothesine hydrochloride in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): a white precipitate is formed (distinction from *ethyl aminobenzoate*, which gives a cherry-red color in a solution containing undissolved benzocaine and from *procaine hydrochloride*, which gives a scarlet precipitate).

Add a few drops of gold chloride solution to an aqueous solution of apothesine hydrochloride (1 in 100): a lemon-yellow precipitate is produced (distinction from *ethyl aminobenzoate* and *procaine hydrochloride* which form brown precipitates).

Dissolve about 0.1 Gm. of apothesine hydrochloride in 5 cc. of water, add 3 drops of diluted sulfuric acid and 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (distinction from *cocaine* which gives a violet precipitate).

Dissolve 0.1 Gm. of apothesine hydrochloride in 1 cc. of sulfuric acid, the solution remains colorless (*organic impurities*).

Dissolve 0.1 Gm. of apothesine hydrochloride in 10 cc. of water and saturate the solution with hydrogen sulfide: no coloration or precipitation is produced (*salts of heavy metals*).

Incinerate about 0.5 Gm. of apothesine hydrochloride, accurately weighed: not more than 0.1 per cent of residue remains.

## PANKE, DAVIS & COMPANY

**Apothesine Hydrochloride (Crystals):** bulk.

**Apothesine Hydrochloride Solution, 1½%:** Each 100 cc. contains 1.5 Gm. of apothesine hydrochloride and 0.5 Gm. of chlorobutanol as a preservative.

**Apothesine Hydrochloride Hypodermic Tablets:** 0.08 Gm.

**Apothesine Hydrochloride and Adrenalin Hypodermic Tablets:** 0.3 Gm. Each tablet contains apothesine hydrochloride 0.3 Gm. and epinephrine hydrochloride 0.0003 Gm., and not more than 0.0003 Gm. of sodium bisulphite.

**Apothesine Hydrochloride and Adrenalin Hypodermic Tablets:** 0.039 Gm. Each tablet contains apothesine hydrochloride 0.039 Gm. and epinephrine hydrochloride 0.00004 Gm., and not more than 0.0003 Gm. of sodium bisulphite.

U. S. patents 1,193,634; 1,193,649; 1,193,650 and 1,193,651 (Aug. 8, 1916; expired).

**BENZYL ALCOHOL.**—*Alcohol Benzylicum.*—Phenylmethylol.— $C_6H_5.CH_2OH$ .—An aromatic alcohol occurring as an ester in tolu and other balsams, the product on the market is produced synthetically.

**Actions and Uses.**—Benzyl alcohol is used as a local anesthetic by injection and by application to mucous membranes. It is practically nonirritant and nontoxic in the ordinary concentrations and doses. (See caution under the general article, *Local Anesthetics*.)

**Dosage.**—Benzyl alcohol is usually used in the form of a 1 to 4 per cent solution in water or physiological solution of sodium chloride. Such solutions may be sterilized by boiling, without danger of decomposition. Pure benzyl alcohol is markedly anti-



acaine hydrochloride (holocaine), and more efficient than a 1 per cent solution of cocaine hydrochloride or a 1 per cent solution of eucaine. The instillation of butacaine sulfate solutions often produces congestion of the conjunctiva, but this does not appear to be of practical significance.

When butacaine sulfate is injected hypodermically into albino rats, the toxicity is two and one-half times that of cocaine, but the lethal dose (injected intravenously into cats) is about equal to that of cocaine. Pharmacologic study indicates that butacaine sulfate may take the place of cocaine, in whole or in part, for surface anesthesia of mucous membranes and that it may be superior for this purpose, especially for use in the eye, to other anesthetics, for the reason that it can be used in materially lower concentrations (presumably because of more prompt absorption). On the other hand, it does not appear promising for injection anesthesia or for spinal anesthesia, since its toxicity is materially greater than that of procaine hydrochloride; but butacaine sulfate is used for injection anesthesia, in concentrations of 0.1 to 0.4 per cent.

A committee of the Section of Ophthalmology of the American Medical Association (*J. A. M. A.* 78:343 [Feb 4] 1922) reported the successful use of butacaine sulfate in practically all operations on the eye and in some operations on the nose and throat. The committee concluded that butacaine sulfate is more powerful than cocaine, a smaller quantity being required; that it acts more rapidly than cocaine and that the action is more prolonged. So far as the experiences of the committee go, butacaine sulfate in the quantity required is less toxic than cocaine. The committee found butacaine sulfate superior to cocaine in that it produces no drying of the tissues and no change in the size of the pupil and that it has no ischemic effect.

Butacaine sulfate solutions, when instilled in the eye at intervals of three minutes apart, permit operative work within five minutes after the last instillation, producing an anesthesia sufficient to perform all of the commoner operations on the eye. For topical use in nose and throat work, a 2 per cent solution is usually employed. Butacaine sulfate solutions may be sterilized by boiling. (See caution under the general article, Local Anesthetics.)

#### ABBOTT LABORATORIES

Butyn Sulfate (*Crystals*): bulk.

Butyn Sulfate Solution, 2 per Cent.

Butyn Sulfate Tablets: 0.2 Gm

U. S. patent 1,358,751 (Nov. 16, 1920; expired), 1,676,470 (July 10, 1928, expires 1945). U. S. trademark 147,893.

Butyn Sulfate Tablets: 25 mg

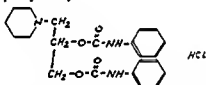
Butyn Sulfate and Epinephrine Hypodermic Tablets:  
Butacaine sulfate 0.01 Gm., epinephrine hydrochloride 0.032 mg.,  
sodium bisulfite, 0.0016 Gm

Ophthalmic Ointment Butyn Sulfate 2%, and Metaphen  
1:3,000. Contains 2 per cent of butacaine sulfate with metaphen  
1:3,000 in a base of petrolatum, 75 per cent and wool fat  
25 per cent

#### MANHATTAN EYE SALVE COMPANY, INC

Butyn Sulfate Ointment, 1%. Butacaine sulfate, 1 per  
cent, water, 1 per cent, wool fat, 5 per cent, and petrolatum  
sterile, 93 per cent. Put up in collapsible tubes for application  
to the eye

panedrol with phenyl isocyanate



*Actions and Uses*—Nearly similar to those of cocaine, but it  
is claimed that the anesthesia lasts somewhat longer than that  
induced by corresponding doses of cocaine hydrochloride or  
procaine hydrochloride. Its toxicity by intravenous injection  
is about three times that of procaine hydrochloride and hence  
it should not be injected except in small amounts.

Solutions of diethane hydrochloride prepared extemporane-  
ously should be used promptly, since such solutions usually  
contain traces of alkali and are thereby subject to precipitation.

*Dosage*—A 1 per cent solution is applied to mucous mem-  
branes. 0.5 per cent solutions may be injected. (See caution  
under the general article Local Anesthetics.)

#### Tests and Standards—

Diethane hydrochloride occurs as a fine white crystalline odorless  
powder. It has a bitter taste followed by a numbness in the  
mouth. It is soluble in water, alcohol, and ether. It is stable  
to light and heat. It is not affected by acids, alkalis, or  
oxidizing agents. It is not affected by carbonates and  
bicarbonates which does not

Dissolve about 0.5 G. separate portions of 5 solution: a white precipitate; to another portion of a 10 per cent solution of 0.2 Gm. hydroxide solution: a an orange color appears of the betanaphthol by responding to the diaz gold chloride solution tion from alypin, apat. give lemon-yellow precipitates, and butyn, procaine and tucocaine, which yield brown hydrochloride in 1 (readily carbonizable hydrochloride dissolution or precipi

Dry about 0.5 G. at 100 C. for six hours; the loss in weight does not exceed 0.5 per cent. Incinerate about 0.5 Gm. of diothane hydrochloride, accurately weighed; the residue is not more than 0.1 per cent. Transfer about 0.3 Gm. of diothane hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 9.5 per cent, nor more than 9.8 per cent when calculated to the dried substance. Dissolve about 0.25 Gm. of diothane hydrochloride, accurately weighed, in 25 cc. of water, by warming, and transfer to a suitable Squibb separatory funnel, rinse twice using about 10 cc. of water, followed by the addition of 3 cc. of a diluted ammonia water (one part of ammonia water and ten parts of water), extract with four successive portions of ether using 20 cc. each; filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; dissolve the oily residue in about 25 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of 10 cc. of water; determine the excess of acid by titration with tenth-normal sodium

the amount to not less propanediol. Transfer the ble solvent th for three cc. of nitric il with correct the pre with diluted ally dry to e calculated an 8.35 per the dried substance

## THE WM. S. MERRELL COMPANY

**Diothane Hydrochloride (Crystals):** bulk.

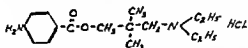
**Ampuls Diothane Hydrochloride 0.5% in Solution of Sodium Chloride 0.6%:** 6 cc.

**Diothane Hydrochloride Solution, 1%:** A solution of diothane hydrochloride, 1 per cent, in distilled water.

U. S. patent 2,004,132 (June 11, 1935; expires 1952). U. S. trade mark 296,850

**LAROCAINE HYDROCHLORIDE** —  $\beta$ -aminobenzoyl-  
—  $\gamma$ -diethyl  
chloride —  
the base of

caine in having a propanol group instead of the ethanol group and has two methyl groups attached to the former



**Actions and Uses**—Larocaine hydrochloride acts as a surface, as well as an infiltration, anesthetic and compares quite favorably in both fields with either cocaine or procaine. Larocaine hydrochloride is quick in action and produces anesthesia of a somewhat longer duration than cocaine or procaine. The average duration of conduction anesthesia is from three to five hours. Larocaine hydrochloride is non narcotic and non habit forming.

**Dosage**—For corneal and conjunctival anesthesia, from 2 to 5 per cent solutions may be used. In otorhinolaryngology, 5 to 10 per cent solutions have been employed. From 0.75 to 1 per cent solutions are used in urology. For conduction anesthesia, 0.25 to 2 per cent solutions may be used. Solutions of tetracaine hydrochloride may be sterilized by boiling for ten minutes. Epinephrine when desired may be added just prior to administration. Stock solutions should be kept in dark bottles. (See caution under the general article Local Anesthetics.)

### Tests and Standards —

[illegible]

Dissolve about 0.05 Gm of tetracaine hydrochloride in 50 cc of water, separate portions of 5 cc each to one portion add 5 cc of

containing



chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 8.8 per cent, nor more than 9 per cent when calculated to the dried substance. Transfer about 0.3 Gm of larocaine hydrochloride, accurately weighed, to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 5 cc. of ammonia water; extract with seven successive portions of ether using 35 cc., 30 cc., 25 cc., 25 cc., 20 cc., 15 cc., and 10 cc., respectively; wash the combined ethereal solution with 15 cc. of water, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; expose over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 20 cc. of previously neutralized alcohol; warm slightly; add 12.5 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with tenth-normal sodium hydroxide solution, using methyl red as an indicator; the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 87 per cent nor more than 89 per cent aminobenzoyldimethyldiethylamino propanol, when calculated to the dried substance. Transfer the ammoniacal aqueous portion from the immiscible solvent extraction to a 400 cc. beaker and place on the steam bath for three hours, add 100 cc. of water, followed by the addition of 10 cc. of nitric acid and 25 cc. of silver nitrate solution, subsequently boil, with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.; the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 115 per cent nor more than 117 per cent when calculated to the dried substance.

## HOFFMANN-LA ROCHE, INC.

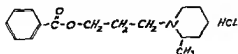
**Larocaine Hydrochloride (Powder):** bulk.

**Tablets Larocaine Hydrochloride:** 0.25 Gm Each tablet contains larocaine hydrochloride, 0.25 Gm and boric acid, 0.025 Gm

U. S. patent 1,824,676 (Sept. 22, 1931; expires 1948). U. S. trade mark 283,775.

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group in place of the ethanol group and in not having an amino group attached to the benzene ring. In addition, it possesses an asymmetric carbon atom and is optically inactive. Metycaine hydrochloride is therefore a racemic mixture of the hydrochlorides.



*Actions and Uses*—Metycaine hydrochloride is a local anesthetic which produces prompt anesthesia either by subcutaneous

was found to be approximately three times as toxic as procaine

*Dosage*—For application to the eye metycaine hydrochloride is used in 2 per cent solutions, for nose and throat, 2 to 10 per cent solutions are used, 1 to 4 per cent solutions have been used for urethral anesthesia, for infiltrative anesthesia in small areas solutions of 0.5 to 1 per cent are generally used (See caution under the general article, Local Anesthetics)

#### *Tests and Standards*—

Metycaine hydrochloride occurs as a fine white crystalline odorless powder, when applied to the tongue it possesses a slightly bitter taste followed by a sense of numbness stable in air, freely soluble in water about 1 in 1, soluble in alcohol and chloroform, insoluble in ether and olive oil. Its aqueous solution (1 in 10) is

of heavy metals)

Dry about 0.5 Gm of metycaine hydrochloride accurately weighed over sulfuric acid in a desiccator for 48 hours the loss does not

solution with 15 cc. of water, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; dry over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with twentieth-normal sodium hydroxide solution, using methyl-red as an indicator; the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 86.5 per cent, nor more than 88 per cent benzoyl- $\gamma$ -(2-methylpiperidino) propanol.

### ELI LILLY AND COMPANY

**Ampoules Solution Metycaine Hydrochloride 1%: 1 cc.** Each cc. contains metycaine hydrochloride 0.01 Gm. in physiological solution of sodium chloride.

**Ampoules Solution Metycaine Hydrochloride 2% and Epinephrine (1:25,000): 1 cc.** Each cc. contains metycaine hydrochloride 0.01 Gm., epinephrine 0.04 mg. and thiourea 0.3%, in Ringer's solution.

The thiourea, which is added to the dosage forms containing epinephrine in order to prevent oxidation, complies with the tests and standards given in the chapter on Pharmaceutical Aids.

**Ampoules Solution Metycaine Hydrochloride 2% and Epinephrine (1:50,000): 2.5 cc.** Each cc. contains metycaine hydrochloride 0.02 Gm., epinephrine 0.02 mg., and thiourea 0.15% in Ringer's solution.

**Ampoules Solution Metycaine Hydrochloride 10%: 2 cc.** Each 2 cc. contains metycaine hydrochloride 0.2 Gm in distilled water. To be used for spinal anesthesia.

**Ampoules Solution Metycaine Hydrochloride 20%: 5 cc.** Each 5 cc. contains metycaine hydrochloride 1 Gm in distilled water. To be used for infiltration and regional anesthesia. The solution must be diluted before using.

**Metycaine Hydrochloride Ophthalmic Ointment 4 per Cent:** Metycaine hydrochloride 4 per cent, in a base consisting of liquid petrolatum and wool fat, with small amounts of paraffin, white petrolatum and ceresin.

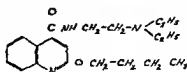
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**Tablets Metycaine Hydrochloride: 0.15 Gm. and 32 mg**

U. S. patent 1,784,903 (Dec. 16, 1930; expires 1947) U. S. trade mark 305,894.

**NUPERCAINE HYDROCHLORIDE.**—Dibucaine—

$\alpha$  chlorocinchoninic acid chloride followed by interaction of the latter with asymmetric diethylethylenediamine and subsequent heating with sodium butylate



**Actions and Uses**—Nupercaine hydrochloride is a local anesthetic acting like cocaine when applied to mucous surfaces and like procaine or cocaine when injected the action being relatively prolonged. Nupercaine hydrochloride is about five times as toxic as cocaine when it is injected intravenously into animals and its anesthetic activity is correspondingly greater than that of cocaine when it is applied to a mucous surface. It is many times more active than procaine hydrochloride when it is injected subcutaneously. It is reported to have caused necrosis of tissue in one case and a condition resembling gangrene with recovery in another. Death has been reported after the subcutaneous injection of 135 cc of a solution of 1 in 1000. Weak solutions (1 in 2000) cause slight temporary vascular dilatation (avoided by the addition of epinephrine hydrochloride) followed by constriction.

**Dosage**—For infiltration anesthesia solutions of from 1 in 2000 to 1 in 1000 with the addition of 0.1 cc of epinephrine hydrochloride solution (1 in 1000) to 100 cc of the solution. Not more than 100 cc of 1 in 1000 solution should be injected. For spinal anesthesia a total of from 7.5 to 10 mg in 1 in 200 solution for sacral anesthesia 25 to 35 cc of 1 in 1000 solution or a correspondingly smaller volume of 1 in 500 solution. Aqueous solutions of nupercaine hydrochloride should be prepared with distilled water as the salts present in tap water of many localities may precipitate the free base butyloxycinchoninic acid diethylethylenediamide. Alkali free glass should be used in the preparation of its solutions. (See caution under the general article Local Anesthetics.)

#### Tests and Standards—

Nupercaine hydrochloride occurs as fine white crystalline odorless powder hygroscopic very soluble in water about 2 in 1 freely soluble in alcohol soluble in acetone and chloroform slightly soluble in benzene ethyl acetate and toluene on warming but with difficulty in the cold. Its aqueous solution about 1 in 20 is faintly alkaline to litmus producing a definite anesthesia on the tongue. Nupercaine hydrochloride melts at 90 to 98 C.

Transfer about 0.3 Gm of nupercaine hydrochloride to a suitable Squibb separatory funnel add 25 cc of water followed by the addition of 2 cc normal sodium hydroxide solution and extract with three successive portions of purified petroleum benzene using 25 cc 20 cc and 10 cc respectively evaporate the combined petroleum benzene extracts to dryness the crystals melt at not less than 64 C. Nupercaine base

fluoresces with the more common oxygen containing acids. Dissolve about 0.5 Gm. of nupercaine hydrochloride in 50 cc. of water, add 0.2 Gm. of potassium perchlorate previously dissolved in 25 cc. of water and

heavy metals).

Dry about 0.5 Gm of nupercaine hydrochloride, accurately weighed, over sulfuric acid in a desiccator for forty-eight hours; the loss does not exceed 2.5 per cent. Incinerate about 0.5 Gm., accurately weighed; the residue is not more than 0.1 per cent. Transfer about 0.5 Gm to a 400 cc. beaker, add 75 cc. of water, followed by the addition of 25 cc. of tenth-normal silver nitrate solution and 10 cc. of nitric acid, subsequently boil, with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride in a Gooch crucible, wash with nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.; the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 95 per cent nor more than 97 per cent, calculated to the dried substance. Transfer about 0.3 Gm., accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 2 cc. of normal sodium hydroxide solution, extract with six successive portions of chloroform, using 50 cc., 25 cc., 20 cc., 15 cc., 10 cc. and 10 cc., respectively, wash the combined chloroformic solution with 15 cc of water and evaporate to a thick oil in a stream of warm air; dry over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with fiftieth-normal sodium hydroxide solution, using methyl red as an indicator. the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 88.5 per cent nor more than 90.5 per cent butylorycinchonine acid diethylethylene diamide, calculated to the dried substance.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

Nupercaine Hydrochloride (*Powder*): 1 Gm and 5 Gm

Ampules Buffered Solution of Nupercaine Hydrochloride 1:200: 2 cc.

Ampules Solution of Nupercaine Hydrochloride 1:1,000: 5 cc and 25 cc.

Ampules Solution of Nupercaine Hydrochloride 1:1,500 in 0.5% Solution of Sodium Chloride: 20 cc.

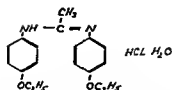
Ampules Solution of Nupercaine Hydrochloride 1:1,000, with Epinephrine, 1:100,000: 2 cc. and 5 cc.

Solution of Nupercaine Hydrochloride 2%.

Tablets Nupercaine Hydrochloride: 50 mg.

U. S. patent 1,825,623. U. S. trademark 266,366

$\text{H}_2\text{O}$  Contains not less than  
 90.5 per cent of phenacaine



For description and standards see the U S Pharmacopeia under Phenacainae Hydrochloridum

**Actions and Uses**—Phenacaine hydrochloride is a local anesthetic like cocaine but having the advantage of a quicker effect. Five minims of a 1 per cent solution when instilled into the eye is usually sufficient to cause anesthesia in from one to ten minutes. This is preceded by temporary smarting.

**Dosage**—It is applied in a 1 per cent aqueous solution. Phenacaine hydrochloride is incompatible with alkalis and their carbonates and the usual alkaloidal reagents. Glass vessels should be avoided in preparing the solution, porcelain being used instead. The solutions are stable as the drug is itself antiseptic. They are not injured by boiling.

#### MANHATTAN EYE SALVE COMPANY, INC

**Holocaine Ointment 1%** Collapsible ophthalmic tubes  
 Holocaine (phenacaine hydrochloride) 1 per cent, water, 1 per cent, wool fat 5 per cent and petrolatum sterile 93 per cent

**Holocaine and Adrenalin Ointment** Collapsible ophthalmic tubes. Composed of holocaine (phenacaine hydrochloride), 1 per cent, adrenalin chloride solution 2 per cent, water 1 per cent, wool fat 10 per cent, white petrolatum sterile 86 per cent.

#### WERNER DRUG & CHEMICAL CO

**Phenacaine Hydrochloride (Powder)** bulk and 1 Gm., 5 Gm., 40 Gm., 150 Gm. and 600 Gm. packages

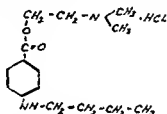
#### WINTHROP CHEMICAL COMPANY, INC

**Holocaine Hydrochloride (Powder)** bulk. Phenacaine hydrochloride

**Holocaine Hydrochloride Solution, 1 per Cent** An aqueous solution containing phenacaine hydrochloride 1 per cent for ocular anesthesia by instillation. The product is not to be used for injection.

**TETRACAINE HYDROCHLORIDE.**—U. S. P.—Pontocaine Hydrochloride.—“When dried over sulfuric acid for 18 hours contains not less than 86.5 per cent and not more than 88.5 per cent of tetracaine ( $C_{15}H_{24}N_2O_2$ ).” U. S. P.

The base of tetracaine hydrochloride belongs to the procaine type. It differs from procaine base in that one of the hydrogens of the paraamino group is replaced by a butyl group, and the two ethyl groups of procaine are replaced by two methyl groups in tetracaine base.



For description and standards see the U. S. Pharmacopœia under *Tetracainæ Hydrochloridum*.

**Actions and Uses.**—Tetracaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride, but it is effective when applied to mucous membranes in lower concentrations. (See caution under the general article, Local Anesthetics.) It is used for surface anesthesia in the eye, nose and throat, and in spinal anesthesia in which the anesthesia is prolonged.

**Dosage.**—Solution of tetracaine hydrochloride, 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. The 1 per cent solution is injected for spinal anesthesia, for which purpose the dose is from 1 to 2 cc. (containing from 10 to 20 mg. of the salt).

#### WINTHROP CHEMICAL COMPANY, INC.

**Ampules Pontocaine Hydrochloride "Niphanoid"** for Spinal Anesthesia: 10 mg. and 20 mg. Ampuls containing tetracaine hydrochloride in finely divided and instantly soluble form. The trade term "Niphanoid" (from the Greek, "snow like") is applied to the process whereby dilute solutions of the drug are subjected to rapid freezing and subsequent evaporation of the solvent under high vacuum; the resultant material is claimed to be more readily soluble.

**Ampules Pontocaine Hydrochloride Solution, 1 per Cent:** 2 cc. Each 2 cc. of solution contains tetracaine hydrochloride 0.02 Gm., sodium chloride 0.0133 Gm., and acetone bisulfite 0.004 Gm.

**Pontocaine Hydrochloride Solution, 0.5 per Cent:** 15 cc. bottles. Contains 0.4 per cent chlorobutanol as a preservative.

**Pontocaine Hydrochloride Solution, 2 per Cent** 30 cc and 120 cc bottles The solution contains 0.4 per cent chlorobutanol as a preservative and is tinted with methylene blue to prevent accidental use for injection

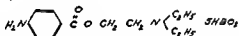
**Pontocaine Hydrochloride Tablets** 0.1 Gm ( $1\frac{1}{2}$  grains) Each tablet contains tetracaine hydrochloride 0.1 Gm boric acid 0.005 Gm acetone sodium bisulfite not more than 0.2 Gm To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology ophthalmology and dentistry

**Pontocaine Base Eye Ointment** An ointment containing 0.5 per cent of tetracaine base, the free base of tetracaine hydrochloride dissolved in white petrolatum

U S patent 1 889 645 (Nov 29 1932 exp res 1949) U S trade mark 282 418

### PROCAINE BORATE — p aminobenzoyl diethylamino

benzoyl diethylaminoethanol



**Actions and Uses**—Procaine borate closely resembles procaine hydrochloride in its actions and uses The molecule is heavier than that of procaine hydrochloride but the toxicity and the anesthetic activity are closely proportional to the procaine base which they contain When injected subcutaneously procaine borate exerts a prompt and powerful anesthetic action It is nonirritant The testimony concerning its activity when applied to mucous membranes lacks uniformity (See caution under the general article Local Anesthetics)

**Dosage**—For infiltration anesthesia solutions of 0.5 to 1 per cent, for blocking nerves from 1 to 2 per cent for tonsillectomy, 0.5 to 1 per cent mucous surfaces 2 to 20 per cent dependent on the location and the depth of anesthesia required Its action is enhanced by the addition of a small amount of epinephrine as in the case of procaine hydrochloride Owing to the smaller content of the base in procaine borate the total dose may exceed that of procaine hydrochloride by about 50 per cent

#### Tests and Standards—

Procaine borate	is a white powder
when mixed with ether	it dissolves
by heating	it decomposes
in ether	it is soluble
hydro	it is soluble



Transfer about 1 Gm. of procaine borate to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 5 cc. of normal sodium hydroxide solution and extract with 3 successive portions of chloroform using 25 cc., 20 cc. and 10 cc., respectively; evaporate the combined chloroformic solutions to dryness, dissolve the oily semisolid base in 25 cc. of a 2 per cent solution of hydrochloric acid; portions of the solution respond to the tests for procaine hydrochloride, U. S. P., XI, p. 306. Dissolve 0.1 Gm. of procaine borate in 2 cc. of methyl alcohol, add 5 drops of sulfuric acid and ignite the mixture; a green mantle is imparted to the flame. Dissolve 0.5 Gm. of procaine borate in 50 cc. of water; separate portions of 10 cc. each yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). When tested for arsenic according to the U. S. Pharmacopeia XI, the product should meet requirements for the arsenic (p. 436, Arsenic Test). Transfer about 0.5 Gm., procaine borate, accurately weighed, to a 50 cc. glass stoppered cylinder, add 25 cc. of chloroform and shake the cylinder and contents for five minutes; allow to stand until the insoluble portion separates; filter, wash the cylinder and the insoluble material onto the filter with two portions of chloroform, using 15 cc. and 10 cc., respectively, adding the washings to the original filtrate; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight over sulfuric acid in a partially exhausted desiccator, the oily residue should not exceed 2 per cent (*limit of uncombined p-aminobenzoyl-diethylaminoethanol*).

Dry about 1 Gm. of procaine borate, accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours; the loss does not exceed 2 per cent. Transfer about 0.4 Gm. of procaine borate to a suitable Squibb separatory funnel,

addition of 2 cc. of normal sodium hydroxide solution, and extract with 3 successive portions of chloroform, using 25 cc., 20 cc. and 10 cc., respectively; evaporate the combined chloroformic solutions to dryness in a stream

of warm air, and dry to constant weight over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol, add 10 cc. of tenth normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with fiftieth normal sodium hydroxide solution, using methyl red as an indicator; the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 50.0 per cent nor more than 52.0 per cent, *p-aminobenzoyl-diethylaminoethanol*, calculated to the dried substance. Transfer about 0.4 Gm. of procaine borate to a steam distillation apparatus and determine the m-boric acid according to the Gladding method of distillation and subsequent titration (See, Leach, Food Inspection and Analysis, ed. 4, p. 884); the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 47.0 per cent nor more than 48.5 per cent, m-boric acid ( $\text{HBO}_2$ ), calculated to the dried substance.

## G. D. SEARLE & Co.

**Tablets Procaine Borate and Epinephrine:** Each tablet contains procaine borate 0.05 Gm. and epinephrine hydrochloride 0.08 mg.

## PROCAINE HYDROCHLORIDE.—Procaine.—U. S. P.

For description and standards see the U. S. Pharmacopeia under *Procainae Hydrochloridum* and the National Formulary under *Ampullae Procainae Hydrochloridi*, *Liquor Procainae Hydrochloridi* and *Tabellae Procainae Hydrochloridi*.

**Actions and Uses**—Procaine hydrochloride is a local anesthetic less toxic than cocaine and most other cocaine substitutes. When injected subcutaneously it exerts a prompt and powerful anesthetic action but the effect is not sustained. This may be remedied by the simultaneous injection of epinephrine. Procaine hydrochloride is only slightly irritant.

It is relatively ineffective when applied to intact mucous membranes. (See caution under the general article, Local Anesthetics.)

**Dosage**—For infiltration anesthesia solutions of 0.25 Gm procaine hydrochloride in 50 or 100 cc isotonic solution of sodium chloride with 0.3 or 0.6 cc. of epinephrine hydrochloride solution (1 in 1000) for instillations and injections solutions of 0.1 Gm procaine hydrochloride in 10 or 5 cc isotonic solution of sodium chloride with or without 0.6 cc of epinephrine hydrochloride solution (1 in 1000). In ophthalmology 1 to 5 or even up to 10 per cent solutions and in rhinolaryngology 5 to 20 per cent solutions are recommended with the addition of 0.4 to 0.5 cc of epinephrine hydrochloride solution (1 in 1000) to each 10 cc.

ABBOTT LABORATORIES

Procaine Hydrochloride (Crystals) bulk

**Ampoules Sterile Procaine Hydrochloride Crystals for Spinal Anesthesia** 50 mg 100 mg 120 mg 150 mg and 200 mg

**Procaine Hydrochloride Tablets** 0.07 Gm 0.15 Gm and 0.2 Gm One tablet dissolved in 4 cc 8 cc or 10 cc of distilled water respectively makes a 2 per cent solution of procaine hydrochloride

**Procaine Hydrochloride Hypodermic Tablets 0.02 Gm  
and 0.05 Gm**

**Procaine Hydrochloride 20 mg Epinephrine 0.016 mg Hypodermic Tablets** Each contains procaine hydrochloride 0.02 Gm epinephrine 0.016 mg sodium bisulfite 16 mg and sodium chloride sufficient so that when the tablet is dissolved in 1 cc of water the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1:60,000 epinephrine hydrochloride.

Epinephrine 0.02 mg  
rocaine hydrochloride  
bisulfite 16 mg and  
tablet is dissolved in

1 cc of water the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1:50,000 epinephrine hydrochloride.

**Procaine Hydrochloride 20 mg., Epinephrine 0.04 mg. Hypodermic Tablets:** Each contains procaine hydrochloride 0.02 Gm., epinephrine 0.04 mg. and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water, the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1:25,000 epinephrine hydrochloride.

**Procaine Hydrochloride Solution 1%:** 100 cc. bottle. Each cc. contains procaine hydrochloride 0.01 Gm., sodium chloride 0.006 Gm., sodium bisulfite 0.001 Gm., and distilled water.

**Ampoule Procaine Hydrochloride Solution 1%:** 1.5 cc. Each ampul contains procaine hydrochloride 0.015 Gm. in chemically pure water with sodium chloride sufficient to make an isotonic solution.

**Ampoules Procaine Hydrochloride Solution 2%:** 1 cc and 5 cc. Each cc contains procaine hydrochloride 0.02 Gm. and sodium chloride 5 mg. in distilled water to make an isotonic solution.

**Procaine Hydrochloride Solution 2%:** 100 cc. vials. Each cc contains procaine hydrochloride 0.02 Gm., sodium chloride 44 mg., sodium bisulfite 1 mg. in sterile distilled water.

**Ampoule Procaine Hydrochloride Solution 10% for Spinal Anesthesia:** 2 cc. Each cc contains procaine hydrochloride 0.1 Gm. in distilled water.

**Ampoule Procaine Hydrochloride 1%—Epinephrine 1:50,000 Solution:** 2 cc. Each cc. contains procaine hydrochloride 0.01 Gm., epinephrine hydrochloride 0.02 mg. and sodium bisulfite 1 mg. in distilled water to make an isotonic solution.

**Ampoule Procaine Hydrochloride 2%—Epinephrine 1:25,000 Solution:** 1 cc. Each cc. contains procaine hydrochloride 0.02 Gm., epinephrine hydrochloride 0.04 mg. and sodium bisulfite 1 mg. in distilled water to make an isotonic solution.

**Procaine Hydrochloride 2%—Epinephrine 1:25,000 Solution:** 100 cc. bottles. Each cc. contains procaine hydrochloride 0.02 Gm., epinephrine hydrochloride 0.04 mg. and sodium bisulfite 1 mg. in distilled water to make an isotonic solution.

**Ampoule Ephedrine Hydrochloride 2½% and Procaine Hydrochloride 1% Solution:** 2 cc.

**Ampoule Ephedrine Hydrochloride 5% and Procaine Hydrochloride 1% Solution:** 1 cc

U. S. patent 1,260,289 (March 26, 1918; expired).

**GEORGE A. BREON & COMPANY, INC**

**Ampul Procaine Hydrochloride Solution 1%, 2 cc** Each cubic centimeter contains 0.01 Gm in physiological solution of sodium chloride

**Ampul Procaine Hydrochloride Solution 2%, 2 cc** Each cubic centimeter contains 0.02 Gm in physiological solution of sodium chloride

**CHEPLIN BIOLOGICAL LABORATORIES, INC**

**Ampule Solution Procaine Hydrochloride 2%, 1 cc** Each cc contains 0.02 Gm procaine hydrochloride chlorobutanol 5 mg in physiological solution of sodium chloride

**Ampule Solution Procaine Hydrochloride 1% and Epinephrine 3 cc** Each cc contains 0.01 Gm epinephrine hydrochloride 0.04 mg chlorobutanol 5 mg and sodium bisulfite 1 mg in physiological solution of sodium chloride

**THE DRUG PRODUCTS COMPANY, INC**

**Hyposols Solution Procaine Hydrochloride 2%, 2 cc** Each cc. contains 0.02 Gm of procaine hydrochloride in physiological solution of sodium chloride

**ENDO PRODUCTS, INC RICHMOND HILL, N. Y.**

**Ampuls Solution Procaine Hydrochloride 2%, W/V 2 cc** Each cubic centimeter contains 0.02 Gm of procaine hydrochloride, 0.005 Gm of chlorobutanol and 0.001 Gm of sodium bisulfite in distilled water

**Ampuls Solution Procaine Hydrochloride 2%, with Epinephrine 1:20,000 3 cc** Each cubic centimeter contains 0.02 Gm of procaine hydrochloride 0.05 of epinephrine 0.005 Gm of chlorobutanol and 0.001 Gm of sodium bisulfite in distilled water

**Solution Procaine Hydrochloride 2%, W/V 30 cc and 100 cc. vials** Each cubic centimeter contains 0.02 Gm procaine hydrochloride 0.005 Gm of chlorobutanol and 0.001 Gm of sodium bisulfite in distilled water

**Solution Procaine Hydrochloride 2%, with Epinephrine 1:25,000 30 cc and 100 cc vials** Each cubic centimeter contains 0.02 Gm of procaine hydrochloride 0.04 mg of epinephrine 0.005 Gm of chlorobutanol and 0.001 Gm of sodium bisulfite in distilled water

**THE LAKESIDE LABORATORIES, INC**

**Procaine Hydrochloride 2%, 30 cc and 100 cc vials** Each cubic centimeter contains procaine hydrochloride 0.02 Gm sodium bisulfite 0.001 Gm and chlorobutanol 5 mg in isotonic sodium chloride solution

**MERCK & Co., INC.**

**Procaine Hydrochloride (Crystals):** bulk.

**THE Wm. S. MERRELL COMPANY**

**Ampuls Solution Procaine Hydrochloride 1%:** 1 cc. and 10 cc. Each cc. contains procaine hydrochloride 0.01 Gm. in physiological solution of sodium chloride.

**Ampuls Solution Procaine Hydrochloride 2%:** 1 cc. and 10 cc. Each cc. contains procaine hydrochloride 0.02 Gm. in physiological solution of sodium chloride. 40 cc. and 160 cc. bottles.

**E. S. MILLER LABORATORIES, INC.**

**Sterile Solution Procaine Hydrochloride 1% W/V:** 30 cc., 50 cc. and 100 cc. vials and 2 cc. and 5 cc. ampuls. Vials preserved with 0.5 per cent chlorobutanol.

**Sterile Solution Procaine Hydrochloride 2% W/V:** 30 cc., 50 cc. and 100 cc. vials and 2 cc. and 5 cc. ampuls. Vials preserved with 0.5 per cent chlorobutanol.

**E. R. SQUIBB & SONS**

**Ampules Sterile Procaine Hydrochloride Crystals for Spinal Anesthesia:** 50 mg., 100 mg., 120 mg., 150 mg., 200 mg. and 500 mg.

**THE UPJOHN COMPANY**

**Hypodermic Tablets Procaine Hydrochloride: 0.05 Gm.** Each contains procaine hydrochloride 0.05 Gm. with sodium chloride as a base. One tablet dissolved in 1 cc. of distilled water makes a 5 per cent solution of procaine hydrochloride.

**Sterile Solution Procaine Hydrochloride 2%:** 30 cc. rubber capped vials and 100 cc. bottles. Each cubic centimeter contains chlorobutanol 5.0 mg., procaine hydrochloride 20 mg., sodium bisulfite 1.0 mg., sodium chloride 84 mg.

**Hypodermic Tablets Procaine Hydrochloride 0.02 Gm. with Epinephrine 0.025 mg.:** Each contains procaine hydrochloride 0.02 Gm., epinephrine 0.025 mg., sodium chloride 0.013 Gm., benzoic acid 0.3 mg., sodium bisulfite 0.125 mg., and boric acid 2.27 mg. One tablet dissolved in 1 cc. of distilled water makes a 2 per cent solution of procaine hydrochloride.

**Solution Procaine Hydrochloride 1% with Epinephrine:** 30 cc. vials. Each cc. contains procaine hydrochloride 10 mg., epinephrine 0.02 mg., sodium bisulfite 2.1 mg., benzoic acid 0.2 mg., sodium chloride 84 mg., normal hydrochloric acid 0.00125 cc. and chlorobutanol not to exceed 5 mg. in distilled water saturated with carbon dioxide.

**Ampoules Solution Procaine Hydrochloride 2% with Epinephrine** 1 cc and 3 cc Each cc contains procaine hydrochloride 20 mg., epinephrine 0.05 mg., sodium bisulfite 2.6 mg., benzoic acid 0.3 mg., sodium chloride 8.3 mg. and normal hydrochloric acid 0.0016 cc in distilled water saturated with carbon dioxide

**Solution Procaine Hydrochloride 2% with Epinephrine** 30 cc vials Each cc contains procaine hydrochloride 20 mg. epinephrine 0.05 mg., sodium bisulfite 2.6 mg., benzoic acid 0.3 mg., sodium chloride 8.3 mg., normal hydrochloric acid 0.0016 cc and chlorobutanol not to exceed 5 mg. in distilled water saturated with carbon dioxide

# U S STANDARD PRODUCTS CO

**Ampul Solution Procaine Hydrochloride 2% with Epinephrine** 1 25 000 1 cc Each cc contains procaine hydrochloride 20 mg. epinephrine hydrochloride 0.04 mg. and sodium bisulfite 0.45 mg. in distilled water

# WINTHROP CHEMICAL COMPANY, INC

**Novocain (Crystals) bulk** Procaine hydrochloride

**Ampules Sterile Crystals Novocain for Spinal Anesthesia** 50 mg., 100 mg., 120 mg. 150 mg. 200 mg. 300 mg. and 500 mg.

**Tablets Novocain** 0.005 Gm

**Novocain 0.01 Gm with 1-Suprarenin Synthetic Bitartrate** 0.2 mg. Tablets

**Novocain Hypodermic Tablets** 0.05 Gm

**Novocain Hypodermic Tablets** 0.2 Gm Each contains procaine hydrochloride 0.2 Gm. and sodium chloride 0.06 Gm.

**Novocain 0.02 Gm. and 1-Suprarenin Synthetic Bitartrate** 0.02 mg. Hypodermic Tablets

**Novocain 0.02 Gm. and 1-Suprarenin Synthetic Bitartrate** 0.05 mg. Hypodermic Tablets

**Novocain 0.05 Gm. and 1-Suprarenin Synthetic Bitartrate** 0.083 mg. Hypodermic Tablets

**Novocain 0.06 Gm. and 1-Suprarenin Synthetic Bitartrate** 0.06 mg. Hypodermic Tablets

**Novocain 0.08 Gm. and 1-Suprarenin Synthetic Bitartrate** 0.06 mg. Hypodermic Tablets

**Novocain 0.1 Gm. and 1-Suprarenin Synthetic Bitartrate** 0.25 mg. Hypodermic Tablets

**Novocain 0.125 Gm. and 1-Suprarenin Synthetic Bitartrate 0.13 mg. Hypodermic Tablets.**

**Novocain-Suprarenin Solution 1 per Cent:** 30 cc. bottles. Each cc. contains procaine hydrochloride 0.01 Gm., epinephrine bitartrate 0.01 mg., sodium chloride 4 mg., potassium sulfate 4 mg.

**Ampules Novocain Solution 1 per Cent:** 2 cc. and 6 cc. Each cc. contains procaine hydrochloride 0.01 Gm. and sodium chloride 0.006 Gm. in distilled water.

**Ampule Novocain Solution 2 per Cent:** 3 cc. Each cc. contains procaine hydrochloride 0.02 Gm. and sodium chloride 4 mg. in distilled water.

**Ampule Novocain Solution 10 per Cent for Spinal Anesthesia:** 2 cc. Each cc. contains procaine hydrochloride 0.1 Gm. in distilled water.

**Ampules Sterile Solution Novocain 20 per Cent:** 1.5 cc. and 5 cc. Each cc. contains procaine hydrochloride 0.2 Gm. in distilled water. This solution must be diluted before use.

**Ampules Novocain Solution 1 per Cent with 1-Suprarenin Synthetic Bitartrate 1:50,000:** 2 cc. and 6 cc. Each cc. contains procaine hydrochloride 0.01 Gm., synthetic epinephrine bitartrate 0.02 mg., sodium chloride 45 mg. and potassium sulfate 4 mg. in distilled water.

**Ampule Novocain Solution 2 per Cent with 1-Suprarenin Synthetic Bitartrate 1:50,000:** 1 cc. Each cc. contains procaine hydrochloride 0.02 Gm. and synthetic epinephrine bitartrate 0.02 mg. in distilled water.

**Ampule Novocain Solution 2 per Cent with 1-Suprarenin Synthetic Bitartrate 1:50,000:** 3 cc. Each cc. contains procaine hydrochloride 0.02 Gm., synthetic epinephrine bitartrate 0.02 mg., sodium chloride 45 mg. and potassium sulfate 4 mg. in distilled water.

**Ampule Novocain Solution 2 per Cent with 1-Suprarenin Synthetic Bitartrate 1:20,000:** 1 cc. and 6 cc. Each cc. contains procaine hydrochloride 0.02 Gm. and synthetic epinephrine bitartrate 0.05 mg. in distilled water.

**Ampule Novocain Solution 2 per Cent with 1-Suprarenin Synthetic Bitartrate 1:20,000:** 3 cc. Each cc. contains procaine hydrochloride 0.02 Gm., synthetic epinephrine bitartrate 0.05 mg., sodium chloride 45 mg. and potassium sulfate 4 mg. in distilled water.

**Ampules Sterile Solution Novocain 20 per Cent with 1-Suprarenin Synthetic Bitartrate 1:9,000:** 1.5 cc. and 5 cc. Each cc. contains procaine hydrochloride 0.2 Gm. and synthetic epinephrine bitartrate 0.11 mg. in distilled water. This solution must be diluted before use.

**Ampules Ephedrine-Novocain Solution** 1 cc and 2 cc  
Each ampul contains procaine hydrochloride 1 per cent and  
ephedrine hydrochloride 5 per cent in sterile distilled water

U. S. patent 812 554 (Feb. 13 1906, expired) U. S. trademark  
53 0-2

**PROCAINE NITRATE.**—*Procaine Nitras*— $C_{11}H_{15}NH_2$   
 $COO C_2H_5$ ,  $N(C_2H_5)_2$ ,  $HNO_3$ . — *p* aminobenzoyl diethylamino  
ethanol mononitrate — 1 *p* aminobenzoxy 2 dimethylaminoethane  
mononitrate —  $\beta$ -diethylaminoethyl-*p* amino benzoate mononitrate

**Actions and Uses.**—The same as those of procaine hydro-  
chloride. It may be prescribed in combination with silver salts  
with which it forms no precipitate. (See caution under the  
general article, Local Anesthetics.)

**Dosage.**—Like that of procaine hydrochloride

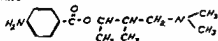
**Tests and Standards.**—

Procaine nitrate occurs in small colorless and odorless crystals soluble  
in water and alcohol. The aqueous solution is neutral in reaction. The  
melting-point is from 100 to 102 C.

If 0.1 Gm. of procaine nitrate is dissolved in 1 cc. of concentrated  
sulfuric acid and a solution of ferrous sulfate carefully floated above  
it a brown zone is formed at the surface of contact of the two solu-  
tions. One part of procaine nitrate dissolved in 10 parts of water and  
acidified with nitric acid should yield no precipitate on the addition of  
silver nitrate solution. It also yields the general tests described under  
procaine hydrochloride.

**TUTOCAINE HYDROCHLORIDE.**—*Butamin*—

$NH_2HCl$ —The base, tutocaine, belongs to the procaine type  
but in addition possesses two asymmetric carbon atoms. It is  
optically inactive. Tutocaine hydrochloride is therefore a  
racemic mixture.



**Actions and Uses.**—Tutocaine hydrochloride is used by sub-  
cutaneous injections, but more especially for surface anesthesia.  
When correctly used, tutocaine hydrochloride rapidly produces  
complete and prolonged anesthesia and is effective even in rela-  
tively low concentration.

It is reported that complete anesthesia of the cornea occurs  
four minutes after the application of 0.25 to 1 per cent solu-  
tions of tutocaine hydrochloride, surface anesthesia in the nose  
throat and eyes is reported to develop more slowly than with  
cocaine, but to be equally intense. When tutocaine hydro-  
chloride is used by injection the effects are very prompt.

In wheel tests on human beings a 1 per cent tutocaine hydro-  
chloride solution produced an anesthesia that lasted for from  
fifteen to twenty minutes. A 0.125 per cent solution containing



epinephrine gave an anesthesia that lasted for about two hours. In experiments made for the council, tutocaine hydrochloride in 3 per cent solution was found to be about four times as toxic as procaine hydrochloride by rapid intravenous injection into the cat. A fatality has been reported following the injection of 8 cc. of a 2 per cent solution into the urethra. (See caution under the general article, Local Anesthetics.) On the other hand, experiments and clinical trials have been reported in support of the claim that tutocaine hydrochloride is relatively safe for use in surface anesthesia and by hypodermic injection.

**Dosage.**—For application to the eye, nose and throat, 2 to 5 per cent solutions of tutocaine hydrochloride are used; for applications to the urethra, 0.5 to 1 per cent solutions, increased to 2 per cent in very painful procedures; for infiltration anesthesia, 0.2 per cent solutions are generally used.

Tutocaine hydrochloride solutions may be sterilized by boiling for a short time.

#### *Tests and Standards.*—

Tutocaine hydrochloride occurs as a light, ivory colored crystalline powder. It is practically odorless; when applied on the tongue, it possesses a faintly bitter taste followed by a sense of numbness; it is stable in air. It is easily soluble in water (about 1 in 4), and difficultly soluble in alcohol (1 in 50). Its aqueous solution (1 in 10) is neutral to litmus paper. It is optically inactive. It melts at from 212 to 215 C. From aqueous solutions, alkali hydroxides and carbonates precipitate the free base, tutocaine, as a light yellowish oil which solidifies on standing and melts at not less than 81 C.

Dissolve about 0.1 Gm. of tutocaine hydrochloride in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of beta naphthol in 10 cc. of sodium hydroxide solution (10 per cent); a scarlet red precipitate is formed (*distinction from phenacaine*, which gives a white precipitate). Dissolve 1 Gm. in 10 cc. of water; separate portions of 2 cc. each of the solutions yield a white precipitate with 1 cc. of gold chloride solution (emon yellow precipitate). Dissolve 0.1 Gm. in 5 cc. of water, add 2 drops diluted hydrochloric acid and 1 cc. of barium chloride solution; no precipitate forms (*distinction from butyn*). To a solution of about 0.1 Gm. in 5 cc. of water, add 3 drops of diluted sulfuric acid and mix with 5 drops of silver nitrate solution; color of the latter disappears. Dissolve about 0.1 Gm.

no coloration or precipitate.

Dry about 1 Gm. of constant weight at 100 C.; the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. accurately weighed; there is not more than 0.2 per cent residue.

Dissolve about 1 Gm. of tutocaine hydrochloride, previously dried and accurately weighed in 15 cc. of water, add a few pieces of ice and 15 cc. of hydrochloric acid and titrate with tenth normal sodium nitrite solution using starch iodide paper as an indicator; the amount of tenth normal sodium nitrite consumed corresponds to not less than 99 per cent nor more than 101 per cent.

WINTHROP CHEMICAL COMPANY, INC

Tablets Tutocaine Hydrochloride, 30 mg with Supra-  
renin Bitartrate 0.15 mg

Tablets Tutocaine Hydrochloride, 30 mg with Supra-  
renin Bitartrate 0.06 mg

Tablets Tutocaine Hydrochloride 50 mg and 100 mg  
U S patent 1 474 567 (Nov 20 1923 expired) U S trademark  
180 610

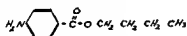
### *Slightly Soluble Local Anesthetics*

The slight solubility of these anesthetics renders them unsuit-  
able for injection but the slow absorption renders them safer  
especially for ulcers wounds, and mucous surfaces. The anes-  
thesia which they induce is usually not so complete as that  
induced by the soluble local anesthetics, but it is more lasting.  
As a group they are practically nonirritant and nontoxic.  
Ethyl aminobenzoate (benzocaine anesthesin) and orthoform  
are about equally effective through intact mucous membranes.  
butyl aminobenzoate (butesin) is claimed to be more effective  
than ethyl aminobenzoate.

They are used for painful wounds ulcers etc of the skin  
and accessible mucous membranes for instance after dental  
operations.

Many if not all local anesthetics occasionally give rise to  
dermatitis. When this is severe the use of the anesthetic  
should be discontinued.

**BUTYL AMINO BENZOATE**—Normal Butyl Amino  
benzoate—U S P—Butesin



For description and standards see the U S Pharmacopeia  
under Butylis Aminobenzoate.

**Actions and Uses**—See preceding article Slightly Soluble  
Local Anesthetics. The actions and uses of butyl aminobenzoate  
are similar to those of ethyl aminobenzoate U S P but it is  
claimed to be more effective.

**Dosage**—Butyl aminobenzoate is used as a dusting powder  
either with or without a diluent. It may be used in the form  
of troches ointment or suppositories or dissolved in a fatty oil.  
Its oil solutions may be sterilized by heat.

ABBOTT LABORATORIES

Butesin (Powder) bulk

U S patent 1 440 652 (Jan 2 1923 expired) U S trademark  
175 095

**BUTESIN PICRATE.**—Dinormalbutyl-*p*-aminobenzoate-trinitrophenol.  $(C_4H_9NH_2COO.C_6H_2)_2.C_6H_2(NO_2)_3.OH$ .—A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-aminobenzoic acid.

**Actions and Uses.**—An aqueous solution of 1 in 2,000 produces immediate and complete anesthesia of the eye which lasts from ten to twenty minutes. Butesin picrate is used in the treatment of burns, ulcers and other denuded painful lesions of the skin.

Instances of butesin picrate dermatitis have occurred which are probably due to idiosyncrasy. A development of a rash following the use of the drug is an indication for its discontinuance.

**Dosage.**—For use, a 1 per cent butesin picrate ointment is proposed.

#### *Tests and Standards.*—

Butesin picrate is a yellow, amorphous powder; odorless; taste slightly bitter. One part of butesin picrate is soluble in 2,000 parts of water; also soluble in 100 parts of cottonseed oil; soluble in alcohol, chloroform, ether and benzene. It melts at 109 to 110 C.

The aqueous solution of butesin picrate is greenish yellow; the color is intensified by the addition of alkali and is decreased by acid. A saturated, aqueous solution of butesin picrate is not affected by the addition of mercuric potassium iodide solution, of silver nitrate solution or of hydrogen sulfide solution. A few drops of sodium nitrate solution added to the acidulated solution of butesin picrate followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon colored precipitate which quickly darkens. A purplish red color is produced if a 1 per cent potassium cyanide solution be added to an aqueous solution of butesin picrate.

Incinerate 0.5 Gm of butesin picrate, accurately weighed, the ash does not exceed 0.1 per cent.

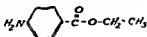
#### ABBOTT LABORATORIES

**Butesin Picrate Ointment with Metaphen:** Butesin picrate 1 per cent, and metaphen 1:5,000, incorporated in an ointment base composed of white wax, paraffin, petrolatum, sodium borate and water, 99 per cent.

**Ophthalmic Ointment Butesin Picrate 1% and Butesin 1%:** Butesin picrate, 1 per cent; butesin, 1 per cent and soft petrolatum, 98 per cent.

U. S. patent 1,596,259 (Aug 17, 1926, expired) U. S. trademark 175,095

**ETHYL AMINOBENZOATE.**—Benzocaine—U. S. P.—Anesthesin



For description and standards see the U. S. Pharmacopoeia under Aethylis Aminobenzoas

*Actions and Uses*—See preceding article, Slightly Soluble Local Anesthetics

*Dosage*—Used as a dusting powder, either with or without a diluent. It may be applied in ointment or in the form of suppositories

ABBOTT LABORATORIES

Anesthesin (Powder) bulk

GEORGE A. BREON & COMPANY, INC., KANSAS CITY, MO

Benzocaine in Oil: Bottles of 15 cc and 480 cc. Contains benzocaine 25 per cent W/V and chlorobutanol 0.5 per cent W/V in cottonseed oil

MERCK & CO., INC.

Benzocaine (Powder) bulk

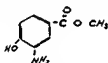
WINTHROP CHEMICAL COMPANY, INC.

Anaesthesin Jelly: 45 cc collapsible tube

Anaesthesin (Powder) bulk

U. S. trademark 55744

**ORTHOFORM**—Orthoform New—Methyl *o*-amino-*p*-hydroxybenzoate— $C_6H_4NH_2OHCOO(CH_3)$ —The *o*-amino-*p*-hydroxybenzoic acid ester of methyl alcohol



*Actions and Uses*—Orthoform is a local anesthetic but penetrates the tissues very slowly on account of its insolubility. It has no action on the unbroken skin. It is practically non-toxic in the usual doses.

It has been applied locally as an analgesic to wounds of every description. It has been used in dentistry and in nasal catarrh, hay fever, etc.

*Dosage*—The Council does not approve of the internal use of this drug. It is used as a dusting powder or mixed with milk sugar for insufflation, dissolved in ether and mixed with oil for pencils, or as an ointment with wool fat, etc.

*Tests and Standards*—

Orthoform occurs in a fine white crystalline powder, neutral in reaction, melting at from 141 to 143 C., odorless and tasteless. It is almost insoluble in water, freely soluble in alcohol and soluble in ether. It is decomposed by boiling with water or by warming with alkalis or their carbonates into methyl alcohol and *o*-paroxybenzoic acid or the alkali salt of it. When crystallized from chloroform it sometimes assumes the form of white crystals melting at from 110 to 111 C. and returning on melting to the ordinary form.

The filtrate obtained after shaking a small quantity of the orthoform with water produces a transient color with ferric chloride and should not give a reaction with silver nitrate. A solution of 0.1 Gm of orthoform dissolved in 2 cc of water by the aid of hydrochloric acid is colored yellowish red on the addition of sodium nitrite and then deposits a yellow precipitate, deepening to red on exposure to the air.

WINTHROP CHEMICAL COMPANY, INC.

**Orthoform (Powder):** bulk.

U S patents 610,348 (Sept. 6, 1898, expired), and 625,158 (May 16, 1899, expired).

## General Anesthetics

**CYCLOPROPANE.**—Cyclopropanum — "Trimethylene" — "Contains not less than 99 per cent by volume of  $C_3H_6$ " — U S P

For description and standards see the U. S. Pharmacopoeia under Cyclopropanum

*Caution*—Cyclopropane is inflammable and its mixture with oxygen or air may explode when brought in contact with a flame or other causes of ignition

*Actions and Uses*—Cyclopropane differs from other gaseous anesthetic agents in that the anesthetic-oxygen ratio is reversed—15 per cent of cyclopropane to 85 per cent of oxygen up to the rarely and briefly used 40 per cent of cyclopropane and 60 per cent oxygen. The high anesthetic potency of cyclopropane as compared with other hydrocarbons makes its use advantageous from the standpoint that abundant concentrations of oxygen may be used. There is evidence to indicate that the rate of diffusion of cyclopropane is about twice that of ethylene. Cyclopropane is eliminated less rapidly than ethylene but much faster than ether. Induction and recovery with cyclopropane are therefore slower than with ethylene but more rapid than with ether.

There is some evidence to indicate that cyclopropane affects the autonomic tissue of the heart more than ether or chloroform. In high concentrations it heightens the irritability of this tissue and predisposes to the occurrence of cardiac arrhythmias. This effect has been shown to be enhanced with the simultaneous use of epinephrine. For these reasons the pulse must be carefully observed and the use of sympathomimetic drugs avoided during cyclopropane anesthesia. Cyclopropane does not stimulate respiration as do many other general anesthetic agents, and for this reason preoperative sedation with respiratory depressants must be used with caution. The signs of Guedel for other anesthetic agents do not apply to cyclopropane, so that familiarity with the signs of the stages of anesthesia for cyclopropane is absolutely essential in the administration of this agent.

The explosibility of cyclopropane-oxygen mixtures is not greater than that of other anesthetic-oxygen mixtures with the

exception of nitrous oxide, but, since the latter gas also supports combustion, its use with cyclopropane should not be regarded as a safeguard against this hazard. Careful operating room technic to avoid conditions conducive to the production of electrostatic sparks and the presence of open flames and the cautery should be observed with the same precautions as those for other anesthetics.

The advantages of cyclopropane consist in its effectiveness in concentrations providing an adequate supply of oxygen, decreased pulmonary irritation (except in asthmatics), less excitement during induction and low toxicity. Its disadvantages include lack of respiratory stimulation, difficulty in detection of the planes of anesthesia by those unfamiliar in its administration and tendency to produce cardiac arrhythmias and postanesthetic headache.

**Dosage**—Cyclopropane is usually furnished in compressed form in metal containers. In use the gas is passed into an inhalation apparatus of the closed circuit type and is then administered by inhalation from a rebreathing bag, always with the admixture of oxygen. The concentration employed varies from 15 to 40 per cent and with the individual patient but should probably not exceed 30 per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen but this should be supplied in quantities adequate for physiologic needs. When other anesthetics are used in combination or when premedication has been employed less cyclopropane is required.

#### THE OHIO CHEMICAL & MFG. CO.

##### Cyclopropane Cylinders

#### E. R. SQUINN & SONS

Cyclopropane 154 liter, 384 liter and 768 liter cylinders

#### ETHYL CHLORIDE—U S P

For description and standards see the U S Pharmacopeia under Aethylis Chloridum, for actions and uses see Useful Drugs under Ethyl Chloride.

**Caution**—*As the vapor is very inflammable Ethyl Chloride must not be used near flame.*

#### MERCCK & Co., INC.

Kelene (liquid) • bulk Ethyl chloride

**ETHYLENE**—Contains not less than 99.0 per cent by volume of  $C_2H_4$ . U S P

For description and standards see the U S Pharmacopeia under Aethylenum.

**Caution**—*Ethylene is inflammable and a mixture of it with oxygen or air will explode when brought in contact with a flame or other causes of ignition.*

*Actions and Uses*—Animal experiments by W. E. Brown (*Canad. M. A. J.*, March 1923, p. 210) and Luckhardt and Carter (*J. A. M. A.* 80:765 [March 17] 1923) indicated that ethylene has a direct action on the nervous system when certain high concentrations of ethylene and corresponding low concentrations of oxygen are used, that the motor reflexes are abolished with these concentrations and that the phenomena produced by the undiluted gas are partly asphyxial, which effect can be removed by addition of oxygen to the ethylene itself.

Trials on human subjects have confirmed the anesthetic and analgesic value of ethylene as demonstrated on animals. First plane surgical anesthesia is stated to be produced easily and analgesia comes on readily and apparently long before surgical anesthesia is established. Given with oxygen, it has been found more powerful than nitrogen monoxide (nitrous oxide) and in most instances as effective as ether; unlike ether it causes minimal respiratory irritation and does not promote mucus secretion.

Extensive use of ethylene in a wide variety of conditions failed to show it to be more explosive than ether-oxygen or ether-nitrous oxide-oxygen under comparable precautions.

Under average conditions of ventilation ethylene, because of its rapid diffusibility, exists in explosive concentration (32 per cent) no further than two feet from the mask. Adequate ventilation of this area should eliminate largely the danger of explosion. No electrical devices should be employed when ethylene is used. The ordinary operating room technique guarding against the presence of open flames, cautery and sparks should be observed.

The advantages of ethylene consist in the production of an equally rapid but more pleasant induction; satisfactory relaxation without cyanosis or sweating; rapid recovery and decreased or absent post-operative nausea. It is useful in older children and in the presence of cardiac, lung or kidney disease, thyrotoxicosis and diabetes.

*Dosage*.—Ethylene is supplied in compressed state in metal containers. For use the gas is passed into an inhalation apparatus and is then inhaled with admixture of oxygen. The concentration employed for surgical anesthesia is never in excess of 90 per cent ethylene with 10 per cent oxygen, though after a prolonged period of anesthesia, a deep anesthetic state may be maintained on 80 per cent or less ethylene. If the patient has been premedicated (morphine, barbital) less ethylene and more oxygen can be given. Mixtures containing over 50 per cent oxygen should never be employed because of the explosion hazard.

**THE CHENEY CHEMICAL CO.**

Ethylene: cylinders.

## PURITAN COMPRESSED GAS CORPORATION

Ethylene: cylinders

## THE OHIO CHEMICAL &amp; MFG CO

Ethylene cylinders

## WALL CHEMICALS CORPORATION

Medical Ethylene Gas cylinders

**TRICHLOROETHYLENE**—Trichloroæthylenum—Trichloroethylene—'Contains not less than 99 per cent and not more than 99.5 per cent of  $C_2HCl_3$ ' U S P

For description and standards see the U S Pharmacopœia under Trichloroæthylenum

*Actions and Uses*—The actions of trichloroethylene have not been extensively investigated. It was introduced into therapeutics as a result of observations of prolonged anesthesia of the fifth nerve following trichloroethylene exposure in industry because it was considered to have a selective action on the sensory endings of the trigeminal nerve. However, evidence is now accumulating which indicates that it is a general anesthetic rather than a specific nerve anesthetic. It must be remembered that the distribution of the fifth nerve is much greater than that of other nerves supplying the face and that trigeminal neuralgia (tic douloureux) while not a common condition is one of the commonest of the facial neuralgias. It is therefore, only natural that the usefulness of this agent in that particular condition should have received such prominence and that the interpretation of the results obtained seemed to indicate a special affinity which did not exist. Regardless of the fact that no special affinity exists, trichloroethylene is a useful measure in the treatment of tic douloureux, as well as in many other painful conditions of the face.

Trichloroethylene has been proposed for use in the prevention and treatment of attacks of angina pectoris. It is believed that trichloroethylene is worthy of trial for this purpose in the clinic, provided patients are under continued medical supervision. Trichloroethylene is a general anesthetic, and its use for this purpose is subject to all the dangers and disadvantages of anesthetics. It should never be prescribed in bulk or taken in large doses, from 1 to 3 cc a day, in divided doses, being ample. The dosage should always be taken with the patient in a reclining position and the material should not be substituted for amyl nitrite or nitroglycerine in the treatment of the acute anginal attack. Each patient should be warned of the possibility of addiction. Excessive dosage of trichloroethylene may mask a severe attack of coronary pain and lead to its being ignored where it should receive immediate medical attention together



with bed rest. It should be used cautiously in the prevention of attacks because it may mask pain indicating exertion beyond the capacity of the heart.

*Dosage.*—One cc. by inhalation, to be repeated after a few minutes if necessary; but it appears probable that not more than 4 cc. should be inhaled within twenty-four hours when it is used for any considerable period of time.

LEDERLE LABORATORIES, INC.

**Trichlorethylene:** 1 cc. sealed fragile glass tubes This product contains not more than 0.2 mg. of ammonium carbonate per cubic centimeter, to prevent the thermal decomposition of the trichlorethylene vapor which occurs during the sealing process.

**VINETHENE.**—*Vinethenum.*—Vinyl Ether for Anesthesia—Merck.— $\text{CH}_2\text{:CH-O-CH:CH}_2$  with the addition of 3.5 per cent absolute alcohol and 0.01 per cent of phenyl- $\alpha$ -naphthylamine

*Caution.*—*Vinethene* is inflammable and deteriorates on exposure to air and light. It should not be used for anesthesia if the original container has been opened longer than twenty-four hours.

*Actions and Uses.*—*Vinethene* is an inhalation anesthetic to be used for short anesthetics. It differs from ether, U. S. P., in the rapidity of its action. This property necessitates special caution in its administration. It is easy to pass from the level of surgical anesthesia to dangerous overdosage; therefore the importance of constant, close observation of the patient cannot be overemphasized. Properly watched, this rapid action is of advantage in short anesthetics, as is the prompt recovery which follows administration of the drug. The patient is completely oriented and ambulant within a few minutes. To prevent recovery from occurring before the surgical procedure is completed, *Vinethene* must be administered continuously during maintenance.

The anesthetist should familiarize himself thoroughly with the properties of *vinethene* before employing it. Of major importance is the fact that the eye signs usually depended on in anesthesia are entirely unreliable. The most important single signs to follow in determining the extent of the anesthesia are the rate, depth, regularity and smoothness of respiration. If the anesthesia is administered in the proper way there should be no cyanosis and the development of such a condition is an indication for the employment of oxygen followed by the use of other anesthetic agents. Although there is occasionally an increased secretion of mucus during maintenance, even when atropine is administered, postoperative complications have not been frequently encountered. Nausea and vomiting occur in about 5 per cent of cases.

Vinethene is intended primarily for use in minor surgical operations of short duration and in dentistry where gas anesthesia is not available. It is also useful as an induction anesthetic. It has been rather extensively used during labor and during postpartum obstetric procedures. It has however, one major disadvantage when used in this branch of medicine—its rapid action has practically precluded its use for obtaining obstetric analgesia.

Under no circumstances should the anesthetic be pushed and if proper relaxation and anesthesia are not obtained with low concentrations other agents should be employed. In case of overdosage respiration is likely to be inhibited and anoxemia and cyanosis are likely to develop. Under such circumstances the anesthetic must be discontinued, oxygen administered, and measures taken to stimulate respiration and provide an adequate airway between the lungs and the atmosphere. The explosive and fire hazards of Vinethene are just about equal to those of ether, U S P.

As with most other anesthetic agents, age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, must be given due consideration as contraindications. It may be administered by the open drop, semioopen drop or closed machine method. It would seem at the present time that the open drop method is preferable, for the short anesthetics. In any case, an adequate oxygen or air supply is essential and an unobstructed airway is of paramount importance.

#### *Tests and Standards —*

Vinethene occurs as a clear colorless liquid with a slight purple fluorescence possessing a characteristic odor. It is miscible with alcohol, chloroform or ether. Vinethene boils at 28.31 C.

Agitate 5 cc. of vinethene in a small chilled glass stoppered cylinder with 2 cc. of water (previously boiled and cooled); the aqueous layer should not affect blue or red litmus paper.

Concentrate 10 cc. of vinethene to about 1 cc. pour on clean odorless filter paper; no foreign odor becomes perceptible as the last portions disappear from the paper and the paper remains odorless.

Add 1 cc. of cold vinethene to 0.5 cc. of a cold solution of 1 Gm. of silver nitrate dissolved in equal parts of 10 cc. of stronger ammonia water and 10 cc. of water and 0.5 cc. of a solution of 1 Gm. of sodium hydroxide dissolved in 10 cc. of water cool in ice, shake for ten seconds, stopper with rubber previously boiled with sodium hydroxide and allow to stand for thirty minutes in ice; no deeper coloration should develop in thirty minutes than in a control prepared by using 1 cc. of benzene previously washed with a 10 per cent solution of sodium hydroxide and 1 cc. of an aqueous solution of 4 cc. of  $\frac{1}{4}$  mol of cobaltous chloride, 4 cc. of  $\frac{1}{4}$  mol of ferric chloride and 8 cc. of  $\frac{1}{4}$  mol of copper sulfate diluted to 100 cc. with water.

To 5 cc. of vinethene add 1 cc. of an alkaline solution of phloroglucinol prepared by dissolving 0.1 Gm. of phloroglucinol in 10 cc. of 20 per cent sodium hydroxide solution and diluting 1 volume with 24 volumes of water; stopper with a rubber stopper previously washed with sodium hydroxide and shake vigorously for three minutes; no darker color should develop than in a control using benzene and similar quantities of the reagent.

Evaporate 10 cc. at room temperature dry at 50 C. the residue should not exceed 0.002 Gm.

MERCK & Co., INC.

**Vinethene:** 10 cc. vials and 25, 50 and 75 cc. bottles.

U. S. patents 2,021,872 (Nov. 19, 1935; expires 1952), 2,044,800 (June 23, 1936; expires 1953), 2,044,801 (June 23, 1936, expires 1953) and 2,099,695 (Nov. 23, 1937; expires 1954). U. S. trademark 297,370.

## Basal Anesthetics

See also Barbituric Acid Derivatives

**SOLUTION OF TRIBROMOETHANOL.**—Solution of Tribromoethyl Alcohol.—U. S. P.—Avertin with Amylene Hydrate. "A solution of tribromethanol in amylene hydrate containing, in each 100 cc., not less than 99 Gm and not more than 101 Gm. of  $C_2H_5Br_3O$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Liquor Tribromoethanolis*

**Actions and Uses.**—Solution of Tribromoethanol is used for basal anesthesia by rectal administration. It should not be employed in dosage sufficient to cause complete anesthesia. When employed for basal narcosis the amount of inhalation anesthetic necessary to establish and maintain complete anesthesia is diminished. A prolonged period of sleep usually follows termination of inhalation anesthesia; during this after-period careful nursing care and continuous vigilance are necessary to maintain an open airway and to prevent the cyanosis and respiratory failure which sometimes follow. Ephedrine, carbon dioxide, caffeine with sodium benzoate and oxygen therapy are said to be effective antidotes against respiratory and circulatory depression occurring from solution of tribromoethanol.

Contraindications to the use of solution of tribromoethanol (relative or absolute depending on the condition of the patient) include liver or kidney dysfunction, severe cardiac disease,

control of certain convulsive conditions such as tetanus; in the latter condition it is used in repeated doses in conjunction with administration of tetanus antitoxin to control the seizures over a period of several days if necessary. It is useful in breaking a vicious cycle of status asthmaticus.

**Caution**—Solution of Tribromoethanol should never be employed by those inexperienced in its use except under expert supervision.

**Dosage**—For each kilogram of body weight rectal, 0.06 cc (1 minim). U. S. P.

Solution of tribromoethanol is administered rectally in 25 per cent solution in warm distilled water at a temperature not

exceeding 40 C. A small quantity of the solution should be tested with the congo red indicator supplied with the preparation just before administration the color of the solution should match that of an equal amount of distilled water containing an equal quantity of the congo red indicator. If the colors do not match this indicates the presence of irritant hydrobromic acid and dibromacetaldehyde and the solution should be discarded.

The ordinary maximum dose for basal anesthesia is 80 mg of tribromoethanol (40 mg of amylene hydrate) per kilogram of body weight. Often less will be sufficient. In young vigorous persons the dose may sometimes be increased to 90 or 100 mg of tribromoethanol (from 45 to 50 mg of amylene hydrate). A dose of 30 to 50 mg per kilogram is usually sufficient for amnesia and is not accompanied by depression of the respiration or circulation. The dose is usually stated in milligrams of the tribromoethanol component only. As the amylene hydrate adds materially to the narcotic effect it should be kept in mind that, with each dose of tribromoethanol half this dose by weight of amylene hydrate is administered.

The total amount administered should not exceed from 6 to 8 cc of solution of tribromoethanol for women or from 9 to 10 cc for men regardless of weight. Dosage tables are supplied by the firm.

#### WINTHROP CHEMICAL COMPANY INC

**Avertin with Amylene Hydrate (Solution)** Each cc contains tribromoethanol 1 Gm and amylene hydrate 0.5 Gm

U. S. patents 1,572,742 (Feb. 9, 1926 exp. res. 1943) 1,725,054 (Aug. 20, 1929 exp. res. 1946) 1,882,984 (Oct. 18, 1932 exp. res. 1949) U. S. trademark 233,204

## CHAPTER IV

### ANTI-INFECTIVES

#### LOCAL ANTI-INFECTIVES

##### Alcohols

**ISOPROPYL ALCOHOL.**—Propan-2-ol— $\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$ .—Obtained by the reduction of acetone or, as a product in the petroleum industry, by the absorption of olefin gases containing propylene in sulfuric acid, and hydrolyzing the resulting sulfuric acid esters.

*Actions, Uses and Dosage.*—Isopropyl alcohol, because it is a solvent for creosote, is used in the removal of that substance from the skin as a prophylactic agent against creosote burns. Isopropyl alcohol has been recommended for the disinfection of the skin and of hypodermic syringes and needles. As it is said not to affect the potency of solutions of insulin, it has been employed as a disinfecting agent in connection with the administration of this agent. Until further data are available, isopropyl alcohol should not be relied on to destroy such spore-bearing organisms as *Clostridium tetani*, *Clostridium welchii* or *Bacillus anthracis*. Recent investigations indicate that isopropyl alcohol compares favorably with ethyl alcohol so far as anti-infective action is concerned. It is not potable and should not be given by mouth.

##### *Tests and Standards.*—

Isopropyl alcohol is a clear, colorless, volatile liquid, having a characteristic odor and a slightly bitter taste, miscible with water in all proportions; also miscible with chloroform and ether. It is insoluble in salt solutions and may be recovered from aqueous mixtures by salting out with sodium chloride, sodium hydroxide, etc. Specific gravity at 25 C. from 0.780 to 0.790. Refractive index at 20 C., from 1.3770 to 1.3780. Isopropyl alcohol is volatilized at low temperatures and boils at from 71 to 83 C. It does not affect blue or red litmus paper previously moistened with water when diluted with an equal volume of water.

Shake 20 cc. of isopropyl alcohol in a glass stoppered cylinder with 1 cc. of freshly prepared solution of ammonia silver nitrate and allow to stand in diffused daylight for six hours; the mixture does not become more than faintly opalescent or acquire more than a faint brownish tint (*aldehyde*). To 5 cc. of isopropyl alcohol add 2 cc. of normal sodium hydroxide solution and 5 drops of a 1 per cent aqueous solution of sodium nitroprusside, mix thoroughly, finally make slightly acid with acetic acid; no purplish red color (*acetone*).

Evaporate 100 cc. of isopropyl alcohol in a platinum dish on a water bath, and dry at 100 C.; the residue does not exceed 0.01 per cent.

##### Cresol and Derivatives

Cresols are phenols in which one of the hydrogen atoms has been replaced by  $\text{CH}_3$ . This substitution increases the germi-

cidal efficiency, while the toxicity is not increased at least not in the same ratio. The cresols therefore, possess distinct advantages as disinfectants. In practice, they are much less toxic than phenol, because they are used more diluted but they are far from being "nonpoisonous." Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor, which depends mainly on impurities, their limited solubility in water, and their variable composition and activity.

They may be rendered soluble by the addition of soap, as in the official compound solution of cresol, and in several other ways. The variability is best discounted by the determination of the phenol coefficient that is, the ratio of the germicidal power of the disinfectant to the germicidal power of phenol tested under identical conditions. (The Council has approved the method of the U. S. Public Health Service for determinations of the phenol coefficient. The details of the test are described in *Public Health Reports*, July 8 1921, pp 1559 1564.) A disinfectant three times as active as phenol against *B. typhosus* would have the coefficient 3 (this being about the coefficient of compound cresol solution). Most disinfectants are now sold with a statement of their coefficient. The degree of dilution for disinfection is obtained simply by multiplying by 20 the phenol coefficient, for instance, a disinfectant having the coefficient 3 would be diluted  $3 \times 20 = 60$  times.

The official cresol is a mixture of the three isomers of  $C_6H_4(OH)CH_3$ . The 'higher homologues,' containing two or more methyl groups are generally referred to as cresylic acid. They have a higher disinfectant coefficient.

The toxicity and local actions of the cresols as of other phenols may be diminished by 'masking' the active OH group through replacement of the H by acid radicals.

**CRESATIN-Sulzberger** (Meta-cresylacetate) —  $CH_3C_6H_4O(CH_3CO)$  — The acetic acid ester of metacresol  $CH_3C_6H_4OH$ .

**Actions and Uses** — Cresatin Sulzberger is said to possess antiseptic and analgesic properties and is apparently free from toxic effects. It is said to be useful in the treatment of affections of the nose, throat and ear such as follicular tonsillitis, nasal suppuration due to ethmoid diseases, atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

**Dosage** — Cresatin Sulzberger may be employed either in the pure form or in dilution with oils or alcohol by direct application or spray.

*Tests and Standards—*

Cresatin Sulzberger occurs as a colorless, oily liquid, possessing a characteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents in liquid petrolatum (not over 5 per cent), and in fixed and volatile oils and is volatile with steam.

If 10 cc. of cresatin Sulzberger is shaken for one minute with 100 cc. of water and filtered through a wet filter, the filtrate has a neutral reaction, and does not produce a violet color with ferric chloride solution or a turbidity with silver nitrate solution. If 10 cc. of cresatin is evaporated it leaves after incineration no weighable residue.

SHARP & DOHME, INC.

Cresatin-Sulzberger: Supplied in 30 cc. glass stoppered bottles and as a spray in 120 cc. square flint bottles

U. S. patent 1,031,971 (July 9, 1912; expired). U. S. trademark 80 533

**Detergents***Cationic*

**ZEPHIRAN CHLORIDE.**—A mixture of alkyl dimethyl benzyl ammonium chlorides having the general formula  $C_6H_5CH_2N(CH_3)_2RCl$ , in which R represents a mixture of alkyl radicals from  $C_8H_{17}$  to  $C_{15}H_{31}$

**Actions and Uses**—Zephiran chloride when employed in solutions of the proper dilution is an effective, relatively non-injurious, surface disinfectant which is germicidal for many pathogenic nonsporulating bacteria and fungi after several minutes' exposure. Solutions of zephiran chloride have low surface tension and possess detergent, keratolytic and emulsifying actions, properties which favor penetration and wetting of tissue surfaces. Solutions of ordinary soaps, which are anionic detergents, in concentrations as low as 0.1 per cent may reduce the germicidal activity of zephiran chloride, which is a cationic detergent, unless its application is preceded by careful rinsing of soap cleansed areas to be disinfected. Alcohol diminishes the ionization of ordinary soap solution, so that the inactivating chemical union of soap with the disinfectant is to some extent prevented. For this reason the application of alcohol 70 per cent (by volume) may well follow the use of the soap and water scrub-rinse procedure as carried out in the usual preoperative technic for preparation of the intact skin before application of the disinfectant. Obviously, under such circumstances the use of the tincture is to be preferred, the use of the aqueous solution being restricted to those regions where soap is not ordinarily employed or where alcohol would produce irritation. The careful rinsing of soap also applies to the disinfection of soap cleansed inanimate objects such as surgical instruments.

Solutions of zephiran chloride are said to have an emollient action and to be relatively nonirritating in effective concentrations. Solutions are of comparatively low toxicity under

the conditions of use for which they are recommended. Rabbits tolerate from 3 to 5 cc by mouth or 12 cc subcutaneously or intraperitoneally per kilogram of body weight of a 10 per cent aqueous solution. Application to the skin of these animals of various concentrations show that a 1 per cent solution is the highest concentration that may be allowed to remain in contact for twenty-four hours without producing irritation. As with other types of disinfectants zephiran chloride has little sporocidal activity and its germicidal potency is greatly reduced by serum. It should be kept in mind that phenol coefficient values as a basis for comparing the relative efficacy of germicides is subject to erroneous interpretation when applied to conditions of actual use.

Zephiran chloride is suitable for general use in the prophylactic disinfection of the intact skin and mucous membranes and in the treatment of superficial injuries.

It is also used for the disinfection of instruments and rubber articles. A 1 per cent solution is added to zephiran chloride solutions for the storage of metal instruments to prevent corrosion.

**Dosage**—For the preoperative disinfection of the unbroken skin or the treatment of superficial injuries and fungous infections zephiran chloride tincture 1:1000 (tinted or stainless according to preference) is recommended. Zephiran chloride solution is employed in concentrations of from 1:10,000 to 1:2,000 for the preoperative disinfection of mucous membranes and denuded skin from 1:5,000 to 1:2,000 for instillation and irrigation of the eye or vagina and from 1:10,000 to 1:5,000 for widely denuded surfaces. For urinary bladder and urethral irrigation a concentration of not more than 1:20,000 of the aqueous solution is recommended. For retention lavage of the bladder, a concentration not to exceed 1:40,000 should be used. For therapeutic disinfection of deep lacerations the undiluted 1:1,000 aqueous solution may be employed but for the irrigation of infected deep wounds concentrations not to exceed 1:3,000 should be used. For the treatment of infected widely denuded areas with wet dressings the aqueous solution should be used in concentrations of 1:5,000 or less.

For the sterile storage of metallic instruments and rubber articles zephiran chloride solution 1:1,000 is used. For the disinfection of operating room equipment a 1:5,000 concentration of the solution may be employed.

#### *Tests and Standards*—

Zephiran chloride occurs as a colorless or slightly yellow gelatinous material containing from 10 to 20 per cent of water possessing an aromatic odor and a sweet taste. It is soluble in water, alcohol, and glycerol, insoluble in ether. Two cc portions of



with diluted nitric and sulfuric acids, white precipitates with solutions of mercury salts, and a gelatinous precipitate with soap solution.

To 2 cc. of a 1 per cent solution of zephiran chloride, add 2 cc. of ethanol, 0.2 cc. diluted nitric acid and 0.5 cc. of silver nitrate solution: a curdy, white precipitate results which is insoluble in diluted nitric acid but soluble in diluted ammonium hydroxide. Heat approximately 0.1 Gm. of zephiran chloride with a small piece of metallic sodium in a small, soft glass test tube. Break the red hot tube in 10 cc. of distilled water, filter, and to the clear filtrate add a few drops of 10 per cent ferrous sulfate solution. Boil for one minute, add 2 drops of ferric chloride solution and acidify with diluted hydrochloric acid: a finely divided blue precipitate forms. Dissolve approximately 0.2 Gm. of zephiran chloride in 1 cc. of sulfuric acid, add 0.1 Gm. of sodium nitrate and heat on a steam bath for three minutes. Cool the solution, dilute to 10 cc. with water, add 0.5 Gm. of zinc dust and warm for five minutes. Decant 2 cc. of the clear liquid, add 1 cc. of a 5 per cent sodium nitrite solution, cool in ice water and add 1 cc. of G salt dissolved in ammonium hydroxide: a deep orange red color results.

Transfer approximately 15 Gm. of zephiran chloride, accurately weighed, to a wide mouthed weighing bottle and dry in an oven at 100 C. for twelve hours, cool and weigh. Determine the moisture content of the original according to the method of Smith and Bryant (*J. Am. Chem. Soc.*, 57:841, 1935) as follows: Prepare approximately 15 molar acetyl chloride by dissolving 11.8 cc. of acetyl chloride in toluene to make 100 cc. Transfer 10 cc. of this solution to a glass stoppered flask, cool for one minute in ice water and add 1 cc. of pyridine and approximately 0.8 Gm. of zephiran chloride, accurately weighed. Shake the mixture and, after allowing to stand five minutes, add 1 cc. of freshly dried ethanol, followed in five minutes by 25 cc. of absolute ethanol. Shake the solution and, after ten minutes, titrate with 0.5 normal sodium hydroxide using phenolphthalein as an indicator. Make a blank determination on the reagents and subtract it from the determination of the unknown.

Dissolve approximately 5 Gm. of zephiran chloride, accurately weighed, in water to make 100 cc. of solution. Transfer a 10 cc. sample to a 100 cc. flask, add 5 cc. of buffer solution (260 Gm. of sodium acetate and 280 cc. of 30 per cent acetic acid to make 1 liter) and 50 cc. of 0.020 normal potassium ferricyanide. Dilute to 100 cc., mix well and allow to stand for one hour. Filter the mixture through paper and discard the first 20 cc. To the next 50 cc. add 5 cc. of 10 per cent ferrous sulfate solution and 5 cc. of diluted hydrochloric acid. After five minutes add 5 cc. of 10 per cent ferric chloride solution and titrate using starch as an indicator. Calculate the percentage of zephiran chloride by the formula: (50 - blank) x 100 = percentage of zephiran chloride, not less than 97 per cent nor more than 101 per cent, calculated from the dry weight.

Transfer approximately 0.1 Gm. of zephiran chloride, accurately weighed, to a small digestion flask, add 2 cc. sulfuric acid and 0.05 Gm. of metallic selenium. Digest the mixture until decomposition is complete, dilute to 15 cc., make alkaline with sodium hydroxide solution, distil into 0.2 normal acid and titrate the excess acid with 0.02 normal alkali, using methyl red as indicator. The nitrogen content is not less than 3.7 nor more than 4.0 per cent of the dry weight.

Transfer a sample of zephiran chloride, accurately weighed, to a 150 cc beaker and dissolve in 60 cc of 40 per cent ethanol. Add 4 cc. of diluted nitric acid and an excess of 15 per cent silver nitrate solution. After an hour filter the precipitated silver chloride, wash well with 40 per cent ethanol, and dry at 105 C.: the chloride content calculated to the dry weight is not less than 0.55 nor more than 10.1 per cent. Transfer approximately 1 Gm. of zephiran chloride, accurately weighed, to a platinum dish; ignite until constant weight is attained the ash is less than 0.1 per cent.

## WINTHROP CHEMICAL COMPANY INC

## Zephiran Chloride bulk

**Zephiran Chloride Solution 1 1,000** 2 19 liter and 384 liter bottles A distilled water solution of zephiran chloride 0.1 per cent

**Zephiran Chloride Tincture 1 1,000 (Stainless)** 2 19 liter and 384 liter bottles An alcohol acetone aqueous solution containing 0.1 per cent (W/V) zephiran chloride ethyl alcohol 50 per cent and acetone 10 per cent by volume

**Zephiran Chloride Tincture 1 1,000 (Tinted)** 2 19 liter and 384 liter bottles An alcohol acetone aqueous solution containing 0.1 per cent (W/V) of zephiran chloride ethyl alcohol 50 per cent and acetone 10 per cent by volume colored with certified dye (D & C Red No. 39)

U S patents 2 086 585 2 087 131 and 2 087 132 (July 13 1937 expire 1954) and 2 108 765 and 2 111 606 (Feb 15 1938 and April 12 1938 exp re 1955) 2 152 047 (March 28 1939 exp res 1956) U S trademark 333 899

## Dyes

Dyes are used medically as antiseptics as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes can be explained by their bacteriostatic and bactericidal powers. These are often relatively specific.

The dyes which have been introduced in medicine for the most part in the last decade are practically all organic synthetics. Roughly they may be divided into five classes: (1) the azo dyes of which scarlet red medicinal scarlet red sulfonate and dimazon are described in New and Nonofficial Remedies (these have been in use for considerable time); (2) the acridine dyes such as acriflavine hydrochloride (introduced as 'acriflavine') acriflavine base (introduced as 'neutral acriflavine') and proflavine; (3) the fluorescein dyes either as fluorescein or combined with the metal mercury such as mercurochrome soluble and flumerin; (4) the phenolphthalein dyes such as phenolphthalein and phenolsulfonphthalein which are official in the U S Pharmacopeia and the chlorine bromine and iodine substitution products; (5) the triphenylmethane or rosaniline series which comprise a large list of substances used in the industries extensively in laboratory practice and more recently in medicine such as gentian violet crystal violet methyl violet and fuchsin; (6) miscellaneous dyes such as methylene blue (methylthionine chloride U S P). Much confusion has existed concerning the composition of dyes various manufacturers of commercial dyestuffs making similar dyes of varying

composition both qualitatively and quantitatively; usually the commercial dye contains a diluent, such as dextrin or salts, and is judged by tinctorial power. In order to obtain comparable results when employed clinically, the dyes should be of constant composition, preferably without diluent.

### *Azo Compounds*

The azo dyes have been used in medicine for many years—more generally recalled under the name “scarlet R” (scarlet red). The exact constitution of the “scarlet R” dyes which have been used seems to have varied in minor details with different investigators. Chemically they have been azo compounds (that is, they contain the linkage—N:N—) combined with betanaphthol. In New and Nonofficial Remedies, a distinction between two scarlet red compounds has been made; scarlet red medicinal Biebrich is described as toluylazotoluylobetanaphthol; scarlet red sulfonate is described as the sodium salt of azobenzenedisulfonic acid azobetanaphthol; it differs from the former in that the methyl group ( $\text{CH}_3$ —) of toluy radicals has been replaced by sodium sulfonate ( $-\text{SO}_3\text{Na}$ ) groups.

In addition to the scarlet red compounds there is the chemically related diacetylaminoazotoluene (dimazon), which contains only one azo group and has a diacetylamino [ $(\text{CH}_3\text{CO})_2\text{N}$ —] group.

*Actions and Uses.*—Scarlet red medicinal Biebrich and scarlet red sulfonate have been claimed to have a marked power of stimulating the proliferation of epithelial cells.

Opinions are divided as to the clinical value, but the dyes are used to promote the growth of epithelium in the treatment of burns, wounds, chronic ulcers, etc. In chronic ulcers, however, it is requisite that the local circulation be good in order to obtain a permanent result.

*Dosage.*—The scarlet red preparations are generally used in the form of an ointment containing from 4 to 8 per cent of the substance. The 8 per cent ointment is somewhat irritating and should be alternated with a soothing ointment. Dimazon is generally used in the form of a 2 per cent ointment; it is also employed as a dusting powder (mixed with talcum) or as a solution (in oil).

**DIMAZON** — Diacetylaminoazotoluene —  $\text{CH}_3\text{C}_6\text{H}_4\text{N} \cdot \text{N} \cdot \text{C}_6\text{H}_4(\text{CH}_3)\text{N}(\text{CH}_3\text{CO})_2$

*Actions, Uses and Dosage.*—See preceding article, Azo Compounds.

#### *Tests and Standards*—

Dimazon is prepared by the acetylation of aminoazotoluene. It is an orange colored crystalline powder, insoluble in water but readily soluble in alcohol, ether, chloroform, acetone and benzene, oils, fats

and petrolatum. It can be removed from cloth by washing with soap and water. It melts at 75 C.

When hydrolyzed with a dilute alcoholic solution of sodium hydroxide, dimazon loses an acetyl group with formation of the insoluble monoacetylaminooztoluol, which has a melting point of 186 C. Prolonged treatment with an alcoholic alkali solution results in loss of the second acetyl group with formation of aminoazotoluol, melting point 100 C.

Treated with fuming hydrochloric acid, dimazon yields monoacetyl azotoluol which is precipitated on dilution with water. Prolonged heating with the acid forms aminoazotoluol and eventually the hydrochloride of the latter.

If dimazon is boiled with alcohol for a long time, an acetyl group is removed with formation of ethyl acetate which may be recognized by its odor.

#### HEILKRAFT MEDICAL COMPANY

**Dimazon (Powder):** bulk

**Dimazon Ointment:** Dimazon, 2 parts, and petrolatum 98 parts

U. S. trademark 89,119

**SCARLET RED.**—Scarlet Red, Medicinal, Biebrich Scarlet Red—"An azo dye, *o* tolyl azo-*o*-tolyl azo  $\beta$  naphthol" *N F*

For description and standards see The National Formulary under Rubrum Scarlatinum and Unguentum Rubri Scarlatini

**Actions, Uses and Dosage**—See preceding article, Azo Compounds

#### HEILKRAFT MEDICAL COMPANY

**Scarlet Red Salve:** Scarlet red medicinal, 8 parts, eucalyptol, 2 parts, and petrolatum, 90 parts

#### MERCK & Co., INC.

**Scarlet Red Medicinal Biebrich (Powder)** bulk

#### NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Scarlet Red Biebrich Medicinal (Powder)** bulk

**SCARLET RED SULFONATE**—The sodium salt of azobenzenedisulfonic acid azobetanaphthol— $C_6H_4(SO_3Na)N \cdot N C_{10}H_6OH$

**Actions, Uses and Dosage**—See preceding article, Azo Compounds

#### Tests and Standards—

Scarlet red sulfonate is a dark brownish red odorless powder. It is soluble in water, slightly soluble in ether, alcohol and acetone, almost insoluble in chloroform, benzene, fixed oils, fats and petrolatum.

Add diluted hydrochloric acid to a concentrated, aqueous solution of scarlet red sulfonate; red floccules separate from the orange red solution. Add sodium hydroxide solution to a concentrated aqueous solution of the substance; a brownish red precipitate forms. Treat the

substance with concentrated sulfuric acid: a green solution results which becomes blue on the addition of water, and on further dilution, brownish red floccules separate. Dissolve about 0.1 Gm. of the substance in 5 cc. of glacial acetic acid, heat to boiling, add zinc dust and continue the boiling: the liquid becomes almost colorless.

#### NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Scarlet Red Sulfonate (Powder):** bulk.

PARKER, DAVIS & COMPANY

**Scarlet Red Emulsion, 4 per Cent:** Scarlet red sulfonate, 4 parts; alcohol, 4 parts; sterilized quince seed jelly, 92 parts.

**Scarlet Red Ointment, 5 per Cent:** Scarlet red sulfonate, 5 parts; petrolatum containing a small amount of wax, 95 parts.

**Scarlet Red Ointment, 10 per Cent:** Scarlet red sulfonate, 10 parts; petrolatum containing a small amount of wax, 90 parts.

#### Acridine Derivatives

The acridine derivatives are mostly yellow dyes—acridine dyes obtained from coal tar—to which the term "flavine" has been applied ("flavine" should more correctly be applied to a vegetable coloring matter). The representative acridine dyes used in medicine are acriflavine hydrochloride (introduced as "trypaflavine" and "acriflavine"), acriflavine base (introduced as "neutral trypaflavine" and "neutral acriflavine"), and proflavine. In 1912, Ehrlich found that the acridine dye diaminoethylacridinium chloride hydrochloride possessed therapeutic properties when used in trypanosome infections and hence he termed it *trypaflavine*. Later this substance was investigated in England, particularly in regard to its effects as a wound antiseptic, and the name "acriflavine" was applied to it. In a generic sense the terms "trypaflavine" and "acriflavine" have been applied both to acriflavine base and acriflavine hydrochloride. Another closely related substance, diaminoacridine monohydrogen sulfate, was studied also, to which was given the name "proflavine". A considerable number of bacteriologic and clinical reports on these substances have been published. It appears to be established that these dyes possess marked antiseptic and germicidal properties, and on this account they have been employed in a number of pathologic conditions. Acriflavine is registered under U. S. Pat. 1,342,000, and is marketed by license of the

**Actions and Uses**—The antiseptic or bacteriostatic action of acriflavine hydrochloride and proflavine appears to be weakened in the presence of serum. In the treatment of wounds, it is claimed that these drugs are comparatively free from toxic or irritant action on living tissues and that they do not inhibit appreciably the phagocytic action of the leukocytes. Acriflavine

hydrochloride is claimed to exert a specific bactericidal action on the gonococcus. The evidence indicates that it has a greater antiseptic action than proflavine, though its action is slower. Applications of acriflavine hydrochloride acriflavine base and proflavine base are used in the treatment of wounds urethritis gonorrhea eczema conditions requiring the use of the dyes tend to render the urine antiseptic provided the reaction of the secretion be alkaline. The use of acriflavine base rather than acriflavine hydrochloride has been suggested in areas where freedom from irritation (due to the acid reaction of acriflavine hydrochloride and proflavine) is desirable. The intravenous use of acriflavine base has been proposed, but critical evidence for its necessity is lacking.

**Dosage**—In the treatment of wounds the solution generally employed is 1 in 1,000 in physiological solution of sodium chloride, although weaker solutions may be used. In suppurating wounds, this solution is used for syringing and swabbing the wound after free incision for irrigation after providing adequate drainage, and for saturating the gauze with which the wound is finally covered. Evaporation should be prevented by protective dressing. In cavities gauze saturated with the solution may be used as a light packing. Fresh wounds are cleansed thoroughly with the solution, and as much of the solution as possible is left in contact with the injured surfaces. Such wounds may be closed by suture and may be expected to heal by first intention.

In the treatment of open wounds an ointment has been used which contains 1 per cent of proflavine oleate (prepared from proflavine base) in an ointment base composed of equal parts of petrolatum and calcium carbonate. A thick layer of the ointment may be spread on gauze and applied to the surface of the cleansed wound or the ointment may be spread on the wound directly. The primary dressing need not be changed for several days.

In gonorrhea, a strength of 1 in 1,000 in physiological solution of sodium chloride may be used for injection into the urethra. For irrigation, when relatively large quantities are to be used a 1 in 4,000 solution is preferable because it is less irritating, solutions of from 1 in 6,000 to 1 in 10,000 have been used. In throat infections a spray of 1 in 1,000 solution is used. In middle ear suppurations a 1 in 500 solution in 50 per cent alcohol is dropped into the ear or the cavity may be packed with gauze wet with the solution. In gingivitis the mouth is irrigated with a 1 in 1,000 solution. Solutions of acriflavine hydrochloride acriflavine base and proflavine may be boiled or heated in an autoclave to 130 C. without decomposition, but they are sensitive to light and should be stored in amber bottles. Solutions over a week old should be discarded.

**ACRIFLAVINE.**—Acriflavine Base.—Neutral Acriflavine —“A mixture of 2, 8 diamino-10-methylacridinium-chloride and 2, 8 diaminoacridine containing, when dried to constant weight at 100° C., not less than 13.3 per cent and not more than 15.8 per cent of Cl.” *N. F.*

For description and standards see the National Formulary under Acriflavina.

*Actions, Uses and Dosage.*—See preceding article, Acridine Derivatives.

#### ABBOTT LABORATORIES

**Acriflavine (Powder):** bulk.

**Enteric Coated Tablets Acriflavine:** 30 mg. Each tablet is coated with shellac and phenyl salicylate.

**Tablets Acriflavine:** 0.1 Gm.

**Tablets Acriflavine:** 30 mg. One tablet dissolved in 30 cc. of isotonic salt solution makes a 1:1,000 solution

#### NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Acriflavine (Neutral) (Powder):** bulk.

**Acriflavine (Neutral) “Pro Injections”:** 0.5 Gm and 10 Gm vials.

**Enteric Coated Tablets Acriflavine (Neutral):** 32.4 mg. Each tablet is coated with phenyl salicylate containing some keratin

**Tablets Acriflavine (Neutral):** 0.1 Gm

**Acriflavine (Neutral) Troches:** Each troche contains neutral acriflavine, 6 mg.; menthol, 0.6 mg. and sodium chloride, 0.6 mg.

**Ointment Acriflavine (Neutral), 1 Per cent:** Acriflavine, 1 part, dissolved in glycerin, 8 parts, and incorporated with a base composed of hydrous wool fat and petrolatum to make 100 parts.

**ACRIFLAVINE HYDROCHLORIDE.**—“A mixture of the hydrochlorides of 2, 8 diamino-10-methylacridinium chloride and 2, 8 diaminoacridine containing, when dried to constant weight over sulfuric acid, not less than 23 per cent and not more than 24.5 per cent of Cl.” *N. F.*

For description and standards see the National Formulary under Acriflavinae Hydrochloridum

*Actions, Uses and Dosage.*—See preceding article, Acridine Derivatives

ABBOTT LABORATORIES

**Acriflavine Hydrochloride (Powder):** bulk

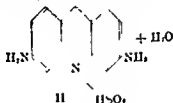
**Tablets Acriflavine Hydrochloride: 30 mg**

NATIONAL ANILINE DIVISION, Allied Chemical & Dye Corporation

**Acriflavine Hydrochloride (Powder):** bulk. Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm shall not exceed 15 mg.

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc contains the quantity to be administered. A series of mice weighing 20 Gm each are injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of 350 mg of the drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose.

**PROFLAVINE.** — Proflavina. — Proflavine Sulfate — 3, 6-diaminoacridinium monohydrogen sulfate — 2, 8-diaminoacridinium monohydrogen sulfate



**Actions, Uses and Dosage**—See preceding article **Verdine Derivatives**

### Tests and Standards —

Proflavine is a reddish-brown, odorless crystalline powder. It is soluble in water and in alcohol, forming brownish solutions which fluoresce on dilution; it is nearly insoluble in ether, chloroform liquid petrolatum, fixed oils and volatile oils.

An aqueous solution of proflavine is neutral to litmus. Add a few drops of hydrochloric acid to an aqueous solution of proflavine which is sufficiently dilute to be fluorescent. The fluorescence disappears but partially reappears on dilution with water. Add 2 drops of sulfuric acid to about 1 cc. of an aqueous solution of proflavine (1 in 250), and agitate the mixture. A brown crystalline precipitate is produced. Under the microscope the crystals are seen to be mostly prismatic needles. An aqueous solution of proflavine (1 in 250) gives a precipitate with barium chloride solution (*distinction from acriflavine*). An aqueous solution of proflavine (1 in 250) gives no precipitate with silver nitrate solution (*distinction from acriflavine*). Add a few drops of formaldehyde solution to 5 cc. of an aqueous solution of proflavine (1 in 250), and immediately add 2 drops of sodium nitrite solution (1 in 10). A violet color is produced. On the further addition of sodium nitrite solution a brownish-violet precipitate is formed and after a few - " " " " " " " " This may be best observed after the filtrate from proflavine (1 in 250) gives - hydrous oxide solution (*distinction*) - precipitates.

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Incinerate about 1 Gm of proflavine accurately weighed the ash amounts to not more than 1 per cent.



## Formaldehyde

The antiseptic actions of formaldehyde cannot be utilized directly on the body because of the irritant and coagulant effects. Attempts have been made to avoid these effects by combining the formaldehyde in such a way as to cause it to be liberated very gradually. The results have been rather disappointing, because it is difficult, if not impossible, to secure just that degree of stability in which the formaldehyde will be liberated in concentrations sufficient to maintain the antiseptic action, but not sufficient to become irritant. Methenamine (hexamethylenetetramine) is a notable exception; but its effects are confined to acid fluids, and, therefore, essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined, rather than through the formaldehyde itself.

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds; with proteins; carbohydrates; amides; phenols and aromatic derivatives. Methenamine does not contain formaldehyde as such, but liberates it under certain conditions (See systemic anti-infectives).

**SOLUTION OF FORMALDEHYDE.**—U. S. P.—Formalin—"An aqueous solution containing not less than 37 per cent of  $\text{CH}_2\text{O}$  with variable amounts of methanol to prevent polymerization." U. S. P.

For description and standards see the U. S. Pharmacopeia under Liquor Formaldehydi

*Actions, Uses and Dosage.*—See Useful Drugs

MERCK & CO., INC.

Solution of Formaldehyde: bulk

SCHERING & GLATZ, INC.

Formalin: bulk.

U. S. trademark 65,625.

## Halogen Compounds

### Chlorine Derivatives

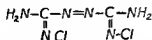
The germicidal action of free chlorine and the hypochlorites is well known. In medicine this action has been utilized by the employment of chlorine water, chlorinated lime and alkaline solutions of sodium hypochlorite (Labarraque's solution), and potassium hypochlorite (Javelle water).

Hypochlorite preparations are fairly stable in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions, an excessive

degree of alkalinity is held to be objectionable on the grounds that it causes destruction of normal tissue and irritation of the skin

On the theory that the action of hypochlorites is dependent on the combination of their active chlorine ( $\text{Cl}+$ ) with the nitrogen of protein, certain organic preparations containing a chloramid group, which are practically neutral and relatively stable, have been proposed as substitutes

**CHLOROAZODIN**—U S P—Azochloramid—Contains the equivalent of not less than 37.5 per cent and not more than 39.5 per cent of active chlorine ( $\text{Cl}$ )' U S P



For description and standards see the U S Pharmacopœia under Chloroazodinum and Liquor Chloroazodini

*Actions and Uses*—Similar to those of a dilute solution of sodium hypochloride, chloramine-T and of dichloramine T except that it does not hydrolyze appreciably in aqueous solutions and that its rate of reaction with mild reducing agents and organic matter in general is low. Consequently its concentration does not decrease rapidly and it is claimed that it exerts a prolonged and strong bactericidal action in the presence of tissue fluids and exudate than the other chloramines. Solutions of chloroazodin are used on dressings for wounds and on packings for infected cavities. Aqueous solutions are suitable for lavage of wounds and for irrigations of and instillations into cavities. It is claimed that short exposure of epithelial tissue to aqueous solutions is harmless and that solutions of chloroazodin in vegetable oil (1:2000) are applicable to the mucous membrane of the vagina, colon and rectum. The available evidence indicates that chloroazodin possesses relatively low toxicity.

*Dosage*—Chloroazodin is usually employed in wounds in a dilution of 1:3300 in an approximately isotonic solution buffered at  $\text{pH}$  7.4. Greater dilutions up to 1:13200 are proposed for use on mucous membranes. On dressings and packings the stable solution containing 1 part of chloroazodin in 500 parts of glyceryl triacetate (triacetin) is used. Gauze impregnated with the triacetin solution of chloroazodin does not dry out and does not stick to the wound. A solution prepared by mixing one volume of a strong solution of chloroazodin in triacetin (1:25) with 19 volumes of a vegetable oil contains one part of chloroazodin in 2000 parts (by weight) of the solution and is claimed to be sufficiently bland to be applicable to certain mucous membranes.

*Tests and Standards.*—

Parasulfonedichloramidobenzoic acid was first prepared by H. D. Dakin and E. K. Dunham (*Brit. M. J.* 1:682 [May 20] 1917) under the name "Halazone."

Halazone is a white powder having a strong odor of chlorine. It is slightly soluble in water and chloroform; insoluble in petroleum ether; soluble in glacial acetic acid, benzene, and with the formation of the salt in alkali hydroxide solutions. It crystallizes in stout prisms from glacial acetic acid. The melting point of pure halazone is 213 C.

Halazone liberates iodine from a sodium iodide solution, and bromine from a sodium bromide solution.

If 15 cc. of a saturated aqueous solution of anilin is treated with 0.05 Gm. of halazone, the solution acquires a brownish red color, which becomes deep blue on supersaturation with ammonia water. If 0.1 Gm. of halazone is treated with a few drops of concentrated sulfuric acid, chlorine is evolved, but no blackening occurs (*readily carbonizable matter.*)

About 0.150 Gm. of halazone (or in the case of halazone tablets, 30 tablets), accurately weighed, is dissolved in from 50 to 100 cc. of water and 10 cc. of a 10 per cent sodium hydroxide solution. Fifteen cc. of a 10 per cent potassium iodide solution is added, and the mixture is then acidified with acetic acid and titrated with tenth normal sodium thiosulfate volumetric solution. (If the reagents used liberate iodine, the number of cubic centimeters of tenth normal sodium thiosulfate volumetric solution required for their decolorization should be deducted from the total volume used.) The chlorine content of halazone should not be higher than 26.26 per cent or lower than 24 per cent. Each cubic centimeter of tenth normal sodium thiosulfate volumetric solution is equivalent to 0.00177 Gm. of active chlorine. The theoretical chlorine content of pure halazone is 26.26 per cent.

**ABBOTT LABORATORIES**

**Halazone (Powder):** bulk

**Tablets Halazone:** Halazone, 4 mg., sodium borate, 11 mg. and sodium chloride sufficient to make about 0.13 Gm.

**HYCLORITE.**—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm., sodium chloride 2.50 Gm., calcium hydroxide 0.14 Gm., inert salts 0.65 Gm. It contains not less than 3.85 per cent of available chlorine.

**Actions and Uses.**—Hyclorite differs from solution of chlorinated soda-U. S. P., chiefly because of the greater content of available chlorine and the lesser degree of alkalinity of the former. It has the actions and uses of solution of chlorinated soda-U. S. P., and when properly diluted it also may be used in the same conditions as those for surgical solution of chlorinated soda-U. S. P. One volume of hyclorite diluted with 7 volumes of water has the same available chlorine content as surgical solution of chlorinated soda, and is isotonic.

**Dosage.**—Hyclorite is used full strength or diluted with 1 or 2 parts of water for direct application to mucous membrane, muscular tissue, bone infections, etc. For irrigation of wounds, throat and body cavities, dilutions of from 1 in 200 to 1 in 2,000 are used. For use in the irrigation method of treating infected wounds, dilute 1 part of hyclorite with 7 parts of water.

The available chlorine content of hyclorite decreases at the rate of about 12 per cent per year. In order that due allowance for this decrease may be made when diluting for use, each bottle of hyclorite bears the date of bottling.

### *Tests and Standards—*

Hyclorite is prepared by decomposing chlorinated lime suspended in water with sodium carbonate.

Hyclorite has the properties of solution of chlorinated soda U S P. It contains no carbonate. When exposed to air, a pellicle forms on its surface owing to the formation of calcium carbonate.

To a definite weight of hyclorite about 5 grams, is added 50 cc of distilled water. To the resulting solution, 10 cc of a 3 per cent hydrogen peroxide solution previously rendered neutral is slowly added. After the reaction is completed which is indicated by the ceasing of the evolution of oxygen, 4 drops of methyl orange indicator solution and an excess (measured) of tenth normal hydrochloric acid are added and then the residual acidity determined by titration with tenth normal sodium hydroxide the alkalinity found corresponds to not more than 0.14 Gm of calcium hydroxide per 100 Gm of hyclorite.

Mix in a flask about 5 cc of hyclorite accurately weighed with 50 cc of distilled water, add 1 Gm of potassium iodide and 5 cc of acetic acid and titrate with tenth normal sodium thiosulfate starch test solution being used as indicator it shows not less than 3.85 per cent of available chlorine.

Each cc. of tenth normal sodium thiosulfate used corresponds to 0.003546 Gm of available chlorine. Due allowance should be made for the decrease in available chlorine content of about 12 per cent per year, date of bottling being stamped on each bottle.

PENNSYLVANIA SALT MANUFACTURING CO (BETHLEHEM LABORATORIES INC., DISTRIBUTOR)

**Hyclorite (Solution) bulk**

U S trademark 120 110

### *Iodine and Iodine Derivatives*

Certain iodine compounds are used for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them, or they may be administered for their systemic actions and for roentgen ray diagnosis.

#### **Iodine Preparations Containing Free Iodine**

**IOCAMFEN**—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

**Actions and Uses**—Iocamfen has the antiseptic and germicidal properties of iodine and the analgesic and stimulating properties of camphor and phenol.

Iocamfen is used especially in the treatment and dressing of wounds, and in dentistry, also in ringworm of the feet, nails, and other parts of the body.

*Dosage.*—Iocamfen is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material.

### *Tests and Standards*—

Iocamfen is a dark, reddish brown, viscid liquid, having a camphoraceous odor. Iocamfen is insoluble in water, but soluble in all proportions in alcohol, ether, benzine and liquid petrolatum.

Iocamfen, like free iodine, interacts with fats and waxes, its free iodine entering into combination.

The free iodine content of iocamfen may be determined thus: About 2 Gm. iocamfen is weighed into a glass-stoppered flask, dissolved in about 25 cc. of chloroform, about 10 cc. of potassium iodide solution (1 in 10) added, and the free iodine determined by titration, under agitation, with tenth normal sodium thiosulfate solution using starch as an indicator.

SCHERING & GLATZ, INC.

**Iocamfen (Liquid):** bulk.

U. S. trademark 112,934

### **Iodine Dusting Powders**

Dusting powders containing iodine in various combinations are used in the treatment of wounds, granulating surfaces, abscess cavities, etc. The clinical results are ascribed to a slight antiseptic action of the iodine, to stimulation of phagocytosis, and to diminished secretion from the wound which renders it a less favorable culture medium for germs.

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform, but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects, they also lack much of the efficiency.

**THYMOL IODIDE.**—“A mixture of iodine derivatives of thymol, principally dithymoldiiodide  $[(C_6H_4.CH_2.C_6H_4.OI)_2]$ , containing, when dried over sulfuric acid for 18 hours, not less than 43 per cent of I” U. S. P.

For description and standards see the U. S. Pharmacopeia under *Thymolis Iodidum*.

MERCK & CO., INC.

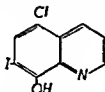
**Thymol Iodide (Powder):** bulk.

WINTHROP CHEMICAL COMPANY, INC.

**Aristol (Powder):** bulk. Thymol iodide.

U. S. trademark 17,393

**VIOFORM.**—5 chloro 7-iodo 8 hydroxyquinoline —  $C_8H_6N$   
 $OH I Cl$ —A substitution compound of 5 chlor 8 hydroxyquino-  
 line resulting from the introduction of one atom of iodine



**Actions and Uses.**—Vioform is used as an almost odorless substitute for iodoform. It is also employed against trichomonis vaginitis and internally against amebiasis. It is used in atopic dermatitis, eczema of the external auditory canal, eczema of the legs, scalp, scrotum and perineum, also in chronic dermatitis, oil dermatitis, acute psoriasis and intertriginous psoriasis.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Entamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. In view of the frequency of persistent infection in the absence of marked symptoms adequate therapy includes re examinations and repetitions of courses of treatment.

**Dosage.**—Vioform is used as a dusting powder for application to wounds, ulcers, burns, exudative skin eruptions, etc. Against amebiasis 0.75 Gm. to 1.0 Gm. daily (in capsules in divided doses of 0.25 Gm. by mouth for 10 days with repetition of the course after a rest period of a week to ten days. A few cases of gastro intestinal irritation with this dosage have been reported, on account of the high iodine content the possibility of iodism should be kept in mind. Until more evidence becomes available, vioform should be used with caution in cases with liver damage.

#### *Tests and Standards.*—

Vioform is a grayish yellow powder having a very faint aromatic odor, almost insoluble in water, sparingly soluble in alcohol, soluble in hot glacial acetic acid.

Boil vioform with a mixture of powdered sodium hydroxide 4 parts and potassium metabisulfite 1 part, cool, add a few drops of glacial acetic acid, allow to crystallize, filter, wash with water, dry, which melt at 178°.

Mix about 0.5 Gm. of vioform accurately weighed in nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potas-

sium nitrate 1 part, and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water, warming to hasten solution; filter into a 400 cc. beaker and wash well. Add 25 cc. of tenth normal silver nitrate (the amount of silver is  $k$  in the formula below); then add slowly, with stirring, nitric acid until acid in reaction to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth-normal potassium sulfocyanate (the amount of silver in the filtrate is  $a$ ). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol, then with ether, dried at 100 C. and weighed ( $w$ ). The amount of iodine can be calculated according to the formula.

$$x = \frac{0.7527 w + a - k}{293}$$

where  $w$  equals combined weight of silver iodide and silver chloride;  $x$  equals weight of silver iodide and ( $w x$ ) equals weight of silver chloride by this method vioform contains not less than 37.5 per cent nor more than 41.5 per cent of iodine, and not less than 11.5 per cent or more than 12.2 per cent of chlorine

## CIBA PHARMACEUTICAL PRODUCTS, INC.

**Vioform (Powder):** bulk.

**Tablets Vioform:** 250 mg

**Vioform Insufflate:** 30 Gm. bottles.

**Vioform Vaginal Inserts:** Each insert contains vioform 250 mg., lactic acid 25 mg, boric acid 100 mg and diluent to make 2 Gm.

U. S. patent 641,491 (Jan. 16, 1900; expired). U. S. trademark 92,732.

## Metal Compounds

### *Bismuth*

The insoluble compounds of bismuth are used for their mechanical action as protectives of inflamed or irritated surfaces. On a wound, a firm crust is formed, beneath which healing proceeds. The drying property of the powder is of chief importance, and the antiseptic action secondary. For the best development of the protective mechanical action, a very fine division of the bismuth compound is essential. This has been secured in various ways. Soluble complex salts of bismuth, which are decomposed by dilute mineral acids with precipitation of insoluble bismuth salts in a very fine state of subdivision, are administered with the expectation that the gastric juice will bring about precipitation and thus protect the digestive tract. It is questionable whether this assumption is realized in many cases. Pharmacologists and many clinicians doubt the usefulness of all soluble bismuth preparations as a means of securing their protective action. On the other hand, the powder is given alone or prepared in a permanent suspension holding the bismuth in such a fine state of division as to favor its deposition evenly throughout the whole intestinal tract.

Bismuth has been combined with other substances either in mixture or in synthetic compounds to produce insoluble compounds which shall be useful as a means of securing convenient administration or of enhancing protective and antiseptic actions. It is doubtful whether combination with antiseptic acids as in bismuth subgallate or bismuth subsalicylate increases the efficiency of the preparation. The antiseptic acids lose their power in alkaline liquids as in the intestines, the introduction of iodine into the benzene nucleus does not increase the antiseptic power. On the other hand bismuth compounds with phenol or with phenols in which bromine or iodine has replaced hydrogen in the benzene ring have an antiputrefactive action.

Soluble compounds of bismuth used for their protective action should be employed with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Skin lesions similar to those sometimes following the use of arsphenamine are among the most important complications of bismuth therapy. For example a pruritus an erythema an urticaria or a dermatitis and rarely hemorrhagic lesions are noted following bismuth therapy, and cases of agranulocytosis with angina have been reported. The administration of the drug should be stopped on the first sign of cutaneous irritation. Bismuth poisoning is indicated by a blue line on the gums and by stomatitis. In some patients undergoing bismuth therapy systemic symptoms of malaise nausea headaches and vague rheumatic muscular and bone pains have been noted. Removal of the bismuth therapy is the principal treatment. Too free local application of bismuth containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by its reduction in the colon.

Most of the bismuth compounds here described (excluding those for use in the treatment of syphilis) belong to the insoluble type. This includes bismuth betanaphtholate bismuth

have some antiseptic power

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Nitrate —  
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with oxide

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For description and standards see the U. S. Pharmacopeia under Bismuthi Subnitratis.

PARKE DAVIS & COMPANY

Bismuth Paste Surgical Bismuth subnitrate 1 part in yellow petrolatum 2 parts



BISMUTH TRIBROMPHENATE — *Tri-  
basic*

**Actions and Uses.**—Bismuth tribromphenate is claimed to be a nonirritant and nontoxic antiseptic. Occasionally cases of sensitization to its local use are noted. It is said to be valuable

**Dosage.**—From 1 to 3 Gm. per day to adults; from 0.125 to 0.3 Gm. as a dose to children. Externally (as a dusting powder, in bandages, etc.) like iodoform, in lotions, and in ointments in 3 to 10 per cent strength.

**Tests and Standards.**—

Bismuth tribromphenate is an amorphous, yellow powder, neutral to moistened litmus paper. It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum, and vegetable oils. Alkalis and strong acid decompose it. It is stable at temperatures below 120 C.

Boil about 1 Gm. of the salt with 10 cc. of sodium hydroxide solution, filter the liquid and acidulate the filtrate with sulfuric acid; the white curdy precipitate produced, when washed and dried, melts at from 90 to 95 C. (*tribromphenol*). The contents of the filter dissolve completely in diluted hydrochloric acid (*insoluble inert material*).

Boil 1 Gm. of bismuth tribromphenate with 20 cc. of a mixture of equal parts of acetic acid and water, cool the solution and filter. Free the filtrate from bismuth by saturating with hydrogen sulfide, boil the mixture and again filter; the latter filtrate leaves not more than 0.005 Gm. of residue on evaporation and gentle ignition (*alkalis and alkali earths*).

Shake 2 Gm. of bismuth tribromphenate, 20 cc. of ether, and 20 cc. of mixture of equal volumes of hydrochloric acid and distilled water in a separatory funnel for one or two minutes. Draw off the aqueous portion and concentrate to about 4 cc.; pour it into 100 cc. of distilled water, filter, evaporate the filtrate on the water bath to 30 cc., again filter and divide this filtrate into portions of 5 cc. each. Mix one portion with an equal volume of diluted sulfuric acid; it does not become cloudy (*lead*). Treat another portion with a slight excess of ammonia water, the supernatant liquid does not exhibit a bluish tint (*copper*), another portion is not immediately affected by barium nitrate test solution (*sulfate*).

Heat gently a mixture of about 0.2 Gm. of bismuth tribromphenate with 5 cc. of potassium hydroxide solution and about 0.2 Gm. of aluminum wire; the vapors evolved do not turn red litmus blue (*nitrates*).

... .. during fifteen

Add 2 cc. of nitric acid to 2 Gm. of bismuth tribromphenate in a porcelain crucible, carefully evaporate to dryness on a sand bath and incinerate. Dissolve the residue in 5 cc. of concentrated hydrochloric acid and add to the solution 10 cc. of a saturated solution of stannous chloride in concentrated hydrochloric acid; the mixture should not darken on standing thirty minutes (*arsenic*).

Mix 0.5 Gm of the salt with 10 cc of a mixture of equal parts of hydrochloric acid and distilled water no effervescence should occur (carbonate)

To about 0.5 Gm of bismuth tribromphenate, accurately weighed add 20 cc of water a combined precipitate and distilled water to slant and heat to constant weight at dull red heat the residue of bismuth oxide ( $\text{Bi}_2\text{O}_3$ ) should not be less than 45 per cent or more than 55 per cent of the original weight of bismuth tribromphenate taken, corresponding to not less than 40 per cent nor more than 49 per cent of bismuth

### SCIERING & GLATZ, INC

Xeroform (Powder): bulk Bismuth tribromphenate

### Mercury

Compounds of mercury are used for the preparation of antiseptic and disinfecting solutions. They have a limited germicidal activity for non sporulating bacteria. They cannot be relied upon to kill bacterial spores even after several hours' exposure. In recent years solutions of compounds of mercury with dyes or other organic radicals have been used extensively in place of mercuric chloride, mercuric cyanide and mercuric iodide for disinfection of the skin, for the treatment of infected wounds and for local treatment of certain bacterial infections. In general these organic compounds of mercury are claimed to be less toxic and less irritating than the older chlorides iodides and cyanides of mercury. They are highly bacteriostatic and hence may be found to be of distinct value as antiseptics even though their germicidal activity, especially for bacterial spores, has not been conclusively demonstrated. Claims for their ability to penetrate deeply into living tissue and to act as efficient chemotherapeutic agents after injection into the blood stream have not been established. Their antibacterial activity is very greatly diminished in the presence of serum or other proteins.

### Inorganic

**MERCURIC CYANIDE** — *Hydrargyri Cyanidum* — *Hydrargyrum Cyanatum* —  $\text{Hg}(\text{CN})_2$  — The mercuric salt of hydrocyanic acid

*Actions and Uses*—Mercuric cyanide has been reported to be as actively antiseptic as mercuric chloride and to be less irritating, but this has been questioned. It is used locally and internally as is mercuric chloride. Blum and Schwab (*Presse Med* 30.1081 [Dec 16] 1922) highly recommended this drug as a diuretic in cardiac (but not in renal) disease. They give

it in doses of 40 to 50 mg. by intravenous or intramuscular injection. They state, however, that mercury should be used as a diuretic only as a last resort when other drugs have failed.

**Dosage.**—Internally, from 4 to 8 mg. locally, solutions of from 1 in 4,000 to 1 in 2,000 may be used for applications to the eye or mucous membranes; from 1.5 to 2 cc. of a 1 per cent solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm. of mercuric cyanide.

In diphtheria and croup, it is used in 0.01 per cent solution as a gargle. In fibrinous rhinitis it is used on a tampon in 0.04 per cent solution.

#### *Tests and Standards.*—

Mercuric cyanide occurs in colorless or white, prismatic crystals, or white powder, odorless and having a bitter, metallic taste (the salt is exceedingly poisonous). It is darkened on exposure to light; is soluble at 15 C. in 12.8 parts of water and in 15 parts of alcohol, in 3 parts of boiling water and in 6 parts of boiling alcohol, and is very sparingly soluble in ether.

When slowly heated it decomposes into metallic mercury with a purple fuming consisting of paracyanogen. If heated in a dry test tube afterward becomes shaped crystals of the salt, the aqueous solution should not yield, on addition of an iodide solution, an excess of the precipitant, nor should it yield a white precipitate on silver nitrate solution (*mercuric chloride*). If mercuric cyanide is dissolved in an aqueous solution of sodium chloride, the addition of phenolphthalein to this solution should produce no red coloration (*mercuric oxide*). Ammonia should not color an aqueous solution blue (*mercuric oxide*). Ammonia water dissolves mercuric cyanide without producing a white precipitate (*oxycyanide*).

#### MALLINCKRODT CHEMICAL WORKS

Mercuric Cyanide (*Powder*): bulk.

#### MERCK & Co., INC.

Mercuric Cyanide (*Powder*): bulk.

**POTASSIUM MERCURIC IODIDE.**—Potassii Hydrargyri Iodidum.—A complex salt,  $K_2HgI_4$ , formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide and containing about 25.5 per cent of mercury.

**Actions and Uses.**—Potassium mercuric iodide is used for the same purposes as mercuric iodide, over which it has some advantages because of its solubility. It is germicidal for many non-sporulating bacteria. However, there seems to be no work to show how much the activity is decreased when an excess

of potassium iodide is present. In comparison with mercuric chloride it is claimed to have a greater safety factor. Weight for weight potassium mercuric iodide is about one half as toxic as mercuric chloride according to animal experiments, in proportion to the mercury content; however, potassium mercuric iodide and mercuric chloride possess about the same toxicity.

Externally, potassium mercuric iodide is used for skin disinfection, irrigations and disinfection of instruments and of excreta and discharges.

*Dosage*—As a disinfectant it is used in concentrations of 1 in 100 to 1 in 10,000. For irrigation of wounds it is desirable to render the solution isotonic by addition of 0.9 per cent sodium chloride. Solutions of potassium mercuric iodide may be prepared:

(1) By dissolving 1 part by weight of mercuric iodide and 1 part by weight of potassium iodide in a small amount of water and then diluting to proper strength, such a solution will contain about 20 per cent excess of potassium iodide sufficient to prevent precipitation of mercuric iodide from dilute solutions of the complex salt. (1 Gm mercuric iodide is equivalent to 1.7 Gm potassium mercuric iodide.)

(2) By dissolving potassium mercuric iodide in water containing potassium iodide. Solutions made from potassium mercuric iodide alone have a tendency to decompose with precipitation of mercuric iodide, hence it is necessary to have present an excess of potassium iodide equivalent to about 20 per cent by weight of the amount of potassium mercuric iodide used.

### *Tests and Standards—*

Potassium mercuric iodide occurs as yellow crystals deliquescent in air. It is soluble in alcohol and in potassium iodide solution. It yields a clear solution with one part of water. When the solution is diluted with much water mercuric iodide precipitates slowly, but if one fifth of its weight of potassium iodide is previously added to the salt or its concentrated solution no mercuric iodide separates on dilution. Its aqueous solution is slightly alkaline to litmus. When the salt is heated in a test tube to the point of fusion it becomes red, but on cooling again assumes a yellow color; at higher temperatures there is volatilization of mercuric iodide.

Treat about 0.2 Gm of potassium mercuric iodide with 1 cc. of water and add 1 cc of chloroform and 0.5 cc of ferric chloride solution; the chloroform shows the characteristic color of iodine. Treat about 0.1 Gm of the salt with 2 cc of sodium hydroxide solution and add a few drops of formaldehyde solution; a black precipitate of metallic mercury is produced.

Potassium mercuric iodide loses not more than 4 per cent of its weight when dried at 120°C for four hours.

Transfer about 1.5 Gm of potassium mercuric iodide accurately weighed to a 100 cc. volumetric flask and dissolve in 15 cc of water; then dilute to 100 cc. Pipette immediately 10 cc of the solution into a glass stoppered 250 cc bottle and add 35 cc of hydrochloric acid and 5 cc. of chloroform. Titrate the solution with tenth normal

potassium iodate (10.701 Gm in 1,000 cc), stoppering the bottle and shaking the contents well after each addition. The addition of the potassium iodate solution is continued until the iodine which was first liberated disappears, and the chloroform shows no pink color: the iodine content, calculated to the dry salt, is not less than 63.4 per cent nor more than 65.5 per cent.

Dissolve about 2.5 Gm of potassium mercuric iodide, accurately weighed, in about 10 cc. of water, and add sufficient potassium iodide solution to prevent precipitation of mercuric iodide. Introduce the solution and washings into a cathode cup, previously weighed with its metallic mercury, and add 10 cc. of sodium hydroxide solution, 20 per cent. Pass through the solution an electric current, gradually increasing the current so that at the end of eight minutes it will be 2 to 3 amperes and 7 to 10 volts, stirring the solution by rotating the anode about 500 revolutions per minute. After forty minutes, wash with distilled water, with the aid of a siphon and without interrupting the current until the current drops to zero. Remove the cathode cup and allow it to stand with 20 cc. of acetic acid solution, 3 per cent, until bubbles cease to be evolved. Wash the mercury with water, and then alcohol, remove most of the excess alcohol by filter paper, then dry in a desiccator over potassium hydroxide sticks and a beaker of mercury. The increase in the weight in the cathode cup represents the amount of mercury present in the quantity of the salt taken. The mercury content of potassium mercuric iodide, calculated to the dry salt, is not less than 25.0 per cent, nor more than 26.0 per cent.

#### DAVIS & GECK, INC.

**Kalmerid Tablets Potassium Mercuric Iodide:** Each tablet contains potassium mercuric iodide 0.5 Gm., potassium iodide 0.37 Gm., ammonium chloride 125 mg. and eosin "Y" 5 mg.

U. S. patent 1,276,119 (Aug. 20, 1918; expired). U. S. trade mark 116,042.

#### PARKE, DAVIS & COMPANY

**Discs of Potassio-Mercuric Iodide:** Each disc represents mercuric iodide 97.2 mg., potassium iodide 97.2 mg. and sodium bicarbonate 2.9159 Gm. Colored blue.

**Discs of Potassio-Mercuric Iodide:** Each disc represents mercuric iodide 24.3 mg., potassium iodide 24.3 mg. and sodium bicarbonate 1.0368 Gm. Colored blue.

**YELLOW MERCURIC OXIDE.**—Yellow Precipitate.—"When dried to constant weight at 110° C., contains not less than 99.5 per cent of HgO."—U. S. P.

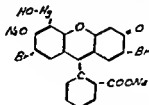
For description and standards see the U. S. Pharmacopeia under Hydrargyri Oxidum Flavum and Unguentum Hydrargyri Oxidi Flavi

#### MANHATTAN EYE SALVE COMPANY, INC.

**Yellow Oxide of Mercury, Adrenalin Chloride, and Phenol Ointment.**—Yellow oxide of mercury, 1 per cent; solution of adrenalin chloride, 2 per cent; menthol, 0.04 per cent; phenol, 0.2 per cent; anhydrous wool fat, 10 per cent, and white petrolatum sufficient to make 100 per cent. Put up in collapsible tubes, for application to the eye.

# Organic

**MERBROMIN** — \ I — **Mercurochrome** — "The disodium salt of 2,7 dibrom 4 hydroxymereurifluorescein. When dried to constant weight at 110° C and assayed Merbromin yields not less than 24 per cent and not more than 26.7 per cent of Hg and not less than 18 per cent and not more than 21.3 per cent of Br' N I"



For description and standards see the National Formulary under Merbrominum, Liquor Merbromini and Liquor Merbromini Chirurgicus.

**Actions and Uses** — Merbromin is a nonirritating moderately active antiseptic. When applied to the skin, mucous membranes and wounds it exerts bacteriostatic and bactericidal action. The 2 per cent aqueous solution of merbromin acts more slowly than tincture of iodine U. S. P. but has more prolonged bacteriostatic effect. The aqueous alcohol acetone solution called surgical solution of merbromin is more rapid in its action than the aqueous solution and may be used for preoperative skin disinfection. Merbromin penetrates significantly only into dying or dead tissue.

The drug is tolerated in a strength of 1 per cent by the bladder, renal pelvis and urethra. A 2 per cent solution applied to the anterior urethra causes only temporary discomfort. When tested by intravenous injection into rabbits the danger point is reached with a dosage of 25 mg. per kg. and 5 mg. causes a decrease in phenolsulfonphthalein excretion and an albuminuria which lasts about a week. Dogs are more resistant. No systemic effects have been observed following its local application in the human. Merbromin has been used in cystitis and urethritis, also in affections of the eye and affections of the ear such as otitis media. Although merbromin has been used intravenously the Council does not recognize the use of the drug for this purpose. The intravenous injection may be followed by severe toxic symptoms.

**Dosage** — In the treatment of infections of the kidney pelvis the ureters are catheterized and the pelvis gently filled with a 1 per cent solution, the catheter is plugged and the solution retained for five minutes. In the treatment of bladder conditions 25 to 30 cc. of the 1 per cent solution is introduced into the bladder and retained for one hour or longer, the

treatment being given daily or on alternate days, or at longer intervals according to circumstances. In anterior gonococcus urethritis, the anterior urethra is filled with a 1 per cent solution and the solution retained for five minutes. If the posterior urethra be involved, the solution is gently retained for an hour or more. In rare cases, considerable irritation is produced, particularly in those with residual urine. Later, in the treatment of acute anterior gonorrhea, a 2 per cent solution is used every three hours. Solutions are self-sterilizing and should not be boiled. They should be made up from the drug itself, as the tablets are not suitable for this purpose.

Merbromin is incompatible with acids, with the salts of most alkaloids and with most local anesthetics. The aqueous solution stains the skin red but the discoloration may be removed by washing in a solution of sodium hypochloride (solution of chlorinated soda).

#### ACES LABORATORY

**Mercurochrome Suppository Aces:** Suppositories containing 2 per cent of merbromin in a slightly aromatized hydro-glycerogelatin base. Each suppository weighs 65 Gm and contains  $\frac{1}{2}$  per cent of a mixture of equal parts of phenol, thymol, eucalyptol and menthol.

#### HYNSON, WESTCOTT & DUNNING, INC.

**Mercurochrome (Powder):** bulk.

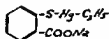
U. S. patent 1,535,003 (April 21, 1925; expired). U. S. trademark 197,189

**Mercurochrome, 2 per Cent Aqueous Solution:**

**Surgical Solution of Mercurochrome:** Merbromin, 2 per cent dissolved in a vehicle consisting of 55 parts of 95 per cent alcohol, 10 parts of acetone, and 35 parts of water, to which has been added sodium carbonate, 0.1 per cent.

**Tablets of Mercurochrome:** 0.3 Gm.

**MERTHIOLATE.**—Merthiolate Sodium.—Sodium ethylmercuri thiosalicylate.— $C_6H_4Hg.SC_6H_4COONa$ . Merthiolate contains from 49.15 to 49.65 per cent of mercury in organic combination



**Actions and Uses.**—Merthiolate is germicidal for many non-sporulating bacteria as demonstrated by the usual laboratory tests and is also fungicidal. It is used for disinfecting tissue surfaces. However, it should be remarked that this agent, like other organic mercurials presently available, cannot be guar-





applicator. After insertion into the vagina the suppository melts at body temperature. The tampon, which is contained in the applicator and is composed of surgical cotton  $1\frac{3}{4}$  inches wide by  $2\frac{3}{4}$  inches long, is released by appropriate pressure on the sleeve of the applicator. The tampon swells by taking up moisture, thus holding the medication in contact with the desired parts. A cord is attached to the tampon for convenient removal.

### ELI LILLY AND COMPANY

**Merthiolate Jelly 1:1,000:** Merthiolate 0.1 per cent, eucalyptol 0.016 per cent and eugenol 0.016 per cent, in a water soluble base.

**Merthiolate Ointment 1:2,000:** Merthiolate 0.05 per cent in a petrolatum base.

**Merthiolate Ophthalmic Ointment, 1:5,000:** Contains merthiolate 1 part in 5,000 parts of a base consisting of liquid petrolatum and wool fat with small amounts of paraffin, white petrolatum and ceresin.

**Merthiolate Solution, 1:1,000:** One gram of merthiolate and 1 Gm. of monoethanolamine in 1,000 cc. of water, buffered with 1.4 Gm. of sodium borate and containing sodium chloride to make the solution approximately isotonic.

**Merthiolate Suppositories, 1:1,000:** Each suppository weighs approximately 10 Gm. and contains merthiolate 1:1,000 in a glycerin and gelatin base consisting of 17.3 parts glycerin and 7.6 parts gelatin.

**Tincture Merthiolate, 1:1,000:** Contains merthiolate, 0.1 Gm., and monoethanolamine, 0.1 Gm., dissolved in alcohol, 50 cc.; acetone, 10 cc., and water, sufficient to make 100 cc.

U. S. Patent 1,672,615 (June 5, 1928; expires 1945) U. S. trademark 252,182.

**METAPHEN.**—The anhydride of 4-nitro-3-hydroxy-mercuri-ortho cresol  $C_6H_3CH_3O \cdot NO_2 \cdot Hg$ . When metaphen is dissolved in alkali solution, the anhydride ring opens, forming the resulting sodium derivative. Metaphen contains from 56 to 57 per cent of mercury in organic combination. It is used only in form of the sodium salt.



**Actions and Uses.**—Metaphen is claimed to be more germicidal than mercuric chloride when tested on cultures of *Staphylococcus aureus* and *Eberthella typhosa*. It is stated to be

relatively nonirritating when applied to mucous membranes or the skin and to be without deleterious action on metallic instruments or rubber. Metaphen is claimed to be relatively non toxic.

Metaphen is proposed for use in the treatment of gonorrhea and infections of the eye, for the disinfection of skin, surgical instruments and rubber if no sporulating pathogenic organisms are present.

**Dosage**—Solutions of metaphen in water are prepared with the aid of sodium hydroxide. For disinfection of instruments solutions of 1 in 5000 to 1 in 1000 for application to the skin solutions of 1 in 5,000 and 1 in 1,000, for ophthalmological and for urethral irrigation solutions of 1 in 5,000 to 1 in 10,000 are proposed.

### Tests and Standards—

Metaphen is a yellow odorless and tasteless substance, insoluble in water almost insoluble in methyl alcohol acetone ether and aqueous sodium carbonate and sodium bicarbonate solution, soluble in dilute aqueous sodium hydroxide solution and in ammonium hydroxide solution, soluble in boiling glacial acetic acid and in nitric acid at room temperature.

Suspend 0.1 Gm. of metaphen in 10 cc. of water, allow to stand for 10 minutes, decantation, dissolve the residue in 10 cc. of water, add 1 cc. of 1 per cent sodium hydroxide solution and heat to boiling, filter and compare the filtrate with the other tube the first tube is no darker than the control (absence of disnitro cresol). Treat 0.1 Gm. of metaphen with 20 cc. of 1 per cent sodium hydroxide solution, no insoluble residue remains (absence of inorganic mercury salts or mercury derivative of nitroindazole).

Transfer about 0.2 Gm. of metaphen accurately weighed to a dry Erlenmeyer flask, add 2 Gm. of potassium permanganate, mix well and then add 5 cc. of diluted sulfuric acid, allow the solution to stand for 15 minutes, then carefully add 15 cc. of sulfuric acid (concentrated) in 2 cc. portions and allow the mixture to stand for another 10 minutes. Decolorize the mixture drop by drop with hydrogen peroxide solution, after decolorization add 5 cc. of water and boil for from five to eight minutes. Cool, add 15 cc. of water and saturate the solution with hydrogen sulfide, keep the solution saturated for 18 hours. Transfer the precipitated mercuric sulfide to a Gooch crucible, wash with hydrogen sulfide water, then with hydrogen sulfide water acidified with sulfuric acid, wash thoroughly with distilled water, then with alcohol and carbon disulfide. The carbon disulfide should remain over the precipitate for approximately one half hour. Wash finally with acetone. Dry in an oven for one half hour at 100 to 110 C. and weigh the mercuric sulfide. The amount of mercury calculated from the weight of the mercuric sulfide is not less than 56 per cent, nor more than 57 per cent in the dried substance.

**ABBOTT LABORATORIES**

**Metaphen Ophthalmic Ointment:** Metaphen 1:3,000 in an ointment base containing anhydrous wool fat, 25 per cent, and petrolatum, 75 per cent.

**Solution Metaphen, 1:500:** Metaphen dissolved in water by means of sodium hydroxide to form the sodium salt of metaphen.

**Solution Metaphen, 1:2,500:** Metaphen dissolved in water containing 0.33 per cent each of sodium bicarbonate and sodium carbonate to form the sodium salt of metaphen.

**Tincture Metaphen, 1:200:** Metaphen, 0.5 Gm., dissolved in a mixture of acetone, 10 cc., water, 40 cc. and alcohol, 50 cc.

U. S. patent reissue 17,563 (Sept. 22, 1925; expired). U. S. trademark 205,507.

**ALLEN LABORATORIES, INCORPORATED**

**Medipax Brand of Vaginal Tampon-Suppositories with Metaphen, 1:2,000:** The suppository contains 225 mg. of Metaphen in 45 Gm. of glycerogelatin, shaped for insertion

*Action and Uses*—A product devised to enable prolonged medication to the upper vaginal vault and cervical region by incorporating a metaphen medicated suppository together with a tampon on a single applicator. After insertion into the vagina the suppository melts at body temperature. The tampon which is contained in the applicator and is composed of surgical cotton  $1\frac{3}{4}$  inches wide by  $2\frac{1}{4}$  inches long is released by appropriate pressure on the sleeve of the applicator. The tampon swells by taking up moisture, thus holding the medication in contact with the desired parts. A cord is attached to the tampon for convenient removal.

**Phenylmercuric Compounds**

Phenylmercuric chloride and basic phenylmercuric nitrate were

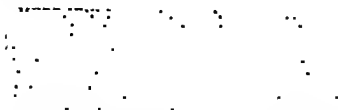
solubility of the salts employed. In acid, neutral or slightly alkaline solutions, chlorides, bromides, iodides and soaps react with phenylmercuric ion to precipitate a phenylmercuric salt. Phenylmercuric chloride is soluble only to the extent of 1 part in 20,000 of water, the bromide is still less soluble and the iodide is quite insoluble. For this reason the chloride has been supplanted by the more soluble basic phenylmercuric nitrate and other salts

The phenylmercuric radical ( $C_6H_5Hg$ )<sup>+</sup> is more stable in acid than in alkaline solutions of its salts. Aqueous solutions con-

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s. In

general, the buffered solutions are **stainless** colorless, odorless without action on rubber and are **noncorrosive** to the common metals other than aluminum, except as these properties may be influenced by the particular acid employed. Solutions of phenylmercuric salts may develop increasing amounts of mercuric and mercurous ions or free mercury, as the result of gradual decomposition of phenylmercuric ions.

There is evidence to indicate that phenylmercuric compounds are of comparatively high germicidal and inhibitory value against a variety of pathogenic bacteria and of relatively low toxicity to human tissue. As with the other types of organic mercurial antiseptics, however, they cannot be depended on to kill bacterial spores even after several hours' exposure. The presence of buffered solutions of phenylmercuric salts does not interfere with the precipitin reaction of human serum, the action of complement, the digestive action of pepsin and trypsin or the antigenic power of vaccine. Despite their relatively low toxicity, phenylmercuric compounds may produce irritation, 'burns' or poisoning in occasional individuals with undue sensitivity. The minimum lethal intravenous dose for rabbits of a 0.067 per cent (1:1,500) aqueous solution of basic phenylmercuric nitrate (buffered with 0.1 per cent boric acid) is 7 cc per kilogram of body weight. Other evidence indicates that the minimum lethal oral dose for these animals is approximately three times the intravenous dose. The toxicity of solutions of this and other phenylmercuric salts may be expected to vary according to the concentration of the solution and the presence of organic matter, which may render them less effective. The appearance of metallic particles in the solution is a sign of decomposition.



of boric acid in appropriate amounts to solutions of phenylmercuric hydroxide.

**Actions and Uses**—Merphenyl borate is recognized for use in tincture form for external use as an antiseptic for the prophylaxis of wounds.

lactic and therapeutic disinfection of the skin, superficial injuries and wounds. Buffered solutions of this compound are claimed to be somewhat less irritating than certain other phenylmercuric compounds.

**Dosage.**—For prophylactic preoperative preparation of the intact skin, disinfection of recent soft tissue injuries and the treatment of superficial wounds a 1:500 tincture of phenylmercuric borate may be applied full strength; for application to mucous membranes, in wet dressings or continuous irrigation for infected wounds a 1:24,000 concentration should be used (prepared by diluting the 1:500 tincture approximately forty-five times with water). In wet dressings, undue concentration of the diluted solution from unavoidable evaporation should be prevented by the addition of about 0.5 per cent of sodium chloride. Approximately  $\frac{1}{2}$  teaspoon of noniodized table salt to each pint of the diluted tincture is recommended. This amount of sodium chloride does not produce excessive precipitation. Dressings and bandages wet with the full strength (1:500) tincture should never be applied.

#### *Tests and Standards.*—

Merphenyl borate tincture 1:500 is a colorless solution which possesses the odor of acetone and alcohol and a pH value of about 5.7. Its specific gravity is between 0.920 and 0.940 at 25 C.

To 2 cc. of merphenyl borate tincture 1:500 add 2 cc. of water and 2 drops of 1 per cent sodium chloride solution; a white precipitate which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid is formed. To 10 cc. of merphenyl borate tincture 1:500 add 2 cc. of saturated sodium chloride solution; a precipitate forms; filter, wash the precipitate with cold water, dry on a porous plate; the melting point is between 248 and 255 C. Evaporate 5 cc. of merphenyl borate tincture 1:500 on a water bath, cool, add 2 cc. of methyl alcohol, ignite the alcohol. The flame is green. To 2 cc. of merphenyl borate tincture 1:500 add 2 cc. of water and 1 cc. of silver nitrate solution; a yellow precipitate forms, soluble in nitric acid.

To 2 cc. of merphenyl borate tincture 1:500 add 2 cc. of water followed by 2 cc. of potassium iodide solution added a drop at a time. a white precipitate forms in the solution that at no time shows traces of orange or red and is insoluble in the excess of potassium iodide (mercuric ions). To 2 cc. of merphenyl borate tincture 1:500 add 2 cc. of ferric ammonium thiocyanate solution. The solution remains colorless. To 2 cc. of merphenyl borate tincture 1:500 add 2 cc. of ferric ammonium sulfate solution. The solution remains colorless. To 2 cc. of merphenyl borate tincture 1:500 add 2 cc. of ferric ammonium sulfate solution and 5 cc. of nitric acid; titrate, using fiftieth normal ammonium thiocyanate delivered from a 10 cc. buret until the color of the solution matches that of a control containing 50 cc. of water, 10 cc. of ferric ammonium sulfate solution, 5 cc. of nitric acid and 0.10 cc. of fiftieth normal ammonium thiocyanate. Subtract 0.10 cc. from the volume noted in the titration; the volume difference is equivalent to not less than 37.5 mg. nor more than 42.5 mg. of phenylmercuric ion ( $\text{C}_6\text{H}_5\text{Hg}^+$ ). (Each cubic centimeter of fiftieth-normal ammonium thiocyanate is equivalent to 5.554 mg. of phenylmercuric ion).

Transfer 25 cc. of merphenyl borate tincture 1:500, accurately measured, to a suitable flask, add 25 cc. of water, 10 cc. of ferric ammonium sulfate solution and 5 cc. of nitric acid; titrate, using fiftieth normal ammonium thiocyanate delivered from a 10 cc. buret until the color of the solution matches that of a control containing 50 cc. of water, 10 cc. of ferric ammonium sulfate solution, 5 cc. of nitric acid and 0.10 cc. of fiftieth normal ammonium thiocyanate. Subtract 0.10 cc. from the volume noted in the titration; the volume difference is equivalent to not less than 37.5 mg. nor more than 42.5 mg. of phenylmercuric ion ( $\text{C}_6\text{H}_5\text{Hg}^+$ ). (Each cubic centimeter of fiftieth-normal ammonium thiocyanate is equivalent to 5.554 mg. of phenylmercuric ion).

## HAMILTON LABORATORIES, INC.

Merphenyl Borate Tincture 1:500 bulk

U S trademark 318 039

**MERPHENYL NITRATE (BASIC)**—Basic Phenyl mercuric Nitrate—A molecular compound of phenylmercuric nitrate and phenylmercuric hydroxide  $C_6H_5HgNO_2 \cdot C_6H_5HgOH$  (M W 634.4)

*Actions and Uses*—Merphenyl nitrate (basic) is recognized for external use in solution or ointment as an antiseptic for the prophylactic and therapeutic disinfection of the skin, superficial abrasions, lacerations wounds and infections

*Dosage*—For prophylactic disinfection of the intact skin and minor lesions the 1:1,500 aqueous buffered solutions may be applied full strength, for application to mucous membranes or for the application of wet dressings or continuous irrigation to wounds, a 1:15,000 to 1:24,000 aqueous solution should be used (prepared by diluting the 1:1,500 buffered solution approximately ten to fifteen times with water) When used as a wet dressing—

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chloride does not produce excessive precipitation The full strength (1:1,500) solution should never be used to wet bandages or dressings The 1:1,500 oxycholesterin base ointment may also be employed for the prophylactic disinfection of minor injuries or may be applied twice daily for the treatment of superficial infections

*Tests and Standards*—

Basic phenylmercuric nitrate is an odorless white crystalline powder, which melts with decomposition between 175 and 185 C. (extremely pure specimens melt as high as 192 C) It is soluble (1:200) in glycerin slightly soluble (1:800) in alcohol and very slightly soluble (1:1,200) in water Its apparent solubility in water is increased if nitric acid or alkalis are present Aqueous solutions of basic phenylmercuric nitrate are incompatible with halides which cause the precipitation of the nearly insoluble halide compounds e.g. phenylmercuric chloride ( $C_6H_5HgCl$ ) The pH of a 0.1 per cent aqueous solution of basic phenylmercuric nitrate is approximately 3.7

Add 3 cc of sulfuric acid to about 0.1 Gm of basic phenylmercuric nitrate the mixture becomes yellow and the odor of nitrobenzene is evolved Add 1 cc of diluted hydrochloric acid to 5 cc of saturated aqueous solution of basic phenylmercuric nitrate a white precipitate forms filter wash the precipitate with cold water dry it on a porous plate the melting point of the product is between 243 and 255 C Solutions of basic phenylmercuric nitrate respond to the U S P test for nitrate Add 5 cc of ammonium sulfide solution to 5 cc of a saturated solution of basic phenylmercuric nitrate there is no reaction in the cold heat the mixture for ten minutes in a boiling water bath a black precipitate forms.

Add 5 cc of sodium hydroxide solution to 5 cc. of a saturated solution of basic phenylmercuric nitrate no yellow precipitate forms (absence of mercuric ions) the solution does not blacken (absence of

*mercurous ions*). Dissolve 0.1 Gm. of basic phenylmercuric nitrate in 150 cc. of water; the solution is colorless and clear.

Ignite (HOOD) 0.5 Gm. of basic phenylmercuric nitrate; the residue does not exceed 0.1 per cent.

Determine the mercury content of an accurately weighed portion of basic phenylmercuric nitrate by a suitable standard method; the mercury content is not less than 62.75 per cent nor more than 63.50 per cent.

Determine the nitrogen content of an accurately weighed portion of basic phenylmercuric nitrate by the *micro Dumas method* or by the method described in the fifth edition of *Methods of Analysis* of the Association of Official Agricultural Chemists, page 27, section 27; the nitrogen content is not less than 2.05 per cent nor more than 2.25 per cent.

Determine the phenylmercuric ion content of 0.2 Gm. of basic phenylmercuric nitrate dissolved in 90 cc. of water and acidified with 10 cc. of concentrated nitric acid. Titrate the solution with twentieth normal ammonium thiocyanate, using 2 cc. of saturated ferric ammonium sulfate solution as the indicator. Compare the color produced against a blank control containing 0.1 cc. of the ammonium thiocyanate solution. Each cubic centimeter of twentieth normal ammonium thiocyanate is equivalent to 0.01389 Gm. of phenylmercuric ion; the phenylmercuric ion content found is not less than 87.0 nor more than 87.9 per cent.

#### HAMILTON LABORATORIES, INC.

**Merphenyl Nitrate (Basic) Solution, 1:1,500:** An aqueous solution of basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent.

**Merphenyl Nitrate (Basic) Ointment, 1:1,500:** A water-in-oil emulsion ( $\frac{2}{3}$  aqueous,  $\frac{1}{3}$  oil phase) of an oxycholesterin base containing basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent.

U. S. trademark 318,039.

**MERPHENYL PICRATE TINCTURE 1:200 WITH PICRIC ACID.**—Tincture of Phenylmercuric Picrate 1:200 with Picric Acid 12%.—A tincture consisting of acetone 10 per cent, alcohol 50 per cent and water 38.3 per cent, containing phenylmercuric picrate 0.5 per cent with picric acid (trinitrophenol) 12 per cent. The tincture can be considered to be a solution of phenylmercuric picrate in a mixture of acetone, alcohol and water. Although a product of the reaction of picric acid and phenylmercuric hydroxide, the picrate may be prepared by the addition of picric acid (trinitrophenol) in appropriate amounts to solutions of phenylmercuric hydroxide.

**Actions and Uses.**—Merphenyl picrate, in an acetone-alcohol tincture with picric acid, is primarily intended as a prophylactic disinfectant in the preoperative preparation of the intact skin and for recent abrasions, lacerations and wounds. It may also be employed in the treatment of superficial infections, particularly when the drying effect of acetone and alcohol is desired. Owing to its staining quality, the picrate compound is useful to delineate the field or area of application. Picric acid is added in sufficient concentration to provide fair stability, but the amount present is also sufficient to exert some disinfectant

action in itself. Because of its high toxicity internally, the possibility of poisoning due to absorption of picric acid from applications of the tincture to large denuded areas of the skin or to mucous membranes should be kept in mind.

**Dosage**—For prophylactic preoperative skin preparation, disinfection of soft tissue injuries and the treatment of superficial infections, tincture of phenylmercuric picrate 1:200 with picric acid 1.2 per cent is applied full strength, in wet dressings or continuous irrigation for infected wounds, a concentration of

to wet dressings or bandages

### Tests and Standards—

Merphenyl picrate tincture 1:200 with picric acid is a strongly yellow colored solution which possesses the odor of acetone and alcohol and a pH value of about 2.0. Its specific gravity is between 0.8980 and 0.901 at 25°C.

To 2 cc of merphenyl picrate tincture 1:200 add 2 cc of water and 2 drops of 1 per cent sodium chloride solution. A white precipitate which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid is formed. To 10 cc of merphenyl picrate tincture 1:200 add 2 cc of saturated sodium chloride solution. A precipitate forms, filter, wash the precipitate with cold water, dry on a porous plate. The melting point of the product is between 248 and 255°C.

To 5 cc of merphenyl picrate tincture 1:200 add 5 cc of water and 2 cc of diluted nitric acid. Extract the solution with three 10 cc portions of ether, combine the ether extracts, filter through a cotton pledget and evaporate. The ether yellow crystals are obtained which melt at from 120 to 123°C.

To 2 cc of merphenyl picrate tincture 1:200 add 2 cc of water followed by 2 cc of potassium iodide solution added a drop at a time. A white precipitate forms in the yellow solution that at no time shows traces of orange or red color and is insoluble in the excess of potassium iodide (*mercuric ions*). To 2 cc of merphenyl picrate tincture 1:200 add an excess of sodium hydroxide solution. The solution becomes orange red but there is no precipitate and the solution does not blacken (*mercurous salts*). To 3 cc of merphenyl picrate tincture 1:200 add 5 cc of sulfuric acid cool overlay with a saturated solution of ferrous sulfate. A brown ring does not appear (*nitrate*).

The mercury content of merphenyl picrate tincture 1:200 can be determined by a suitable electrolytic method. The mercury content is equivalent to not less than 0.26 per cent nor more than 0.28 per cent of merphenyl ion. The merphenyl ion content also may be determined as directed under merphenyl borate tincture 1:500, after removal by ether extraction of the picric acid from an acidified portion of the tincture (nitric acid).

**Caution**—Merphenyl picrate tincture 1:200 with picric acid is more liable to decomposition on aging than certain other phenylmercuric salts.



HAMILTON LABORATORIES, INC.

**Merphenyl Picrate Tincture 1:200 with Picric Acid:**  
bulk.

U. S. trademark 318,039.

### Silver

Silver compounds are used in medicine to secure caustic, astringent and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired, silver nitrate is preferred, because the colloidal compounds of silver are largely or completely lacking in caustic properties. As an astringent, also, silver nitrate is the compound of choice; but it must be used in weaker solutions; silver picrate acts similarly. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds; but when they are not necessary for such purposes, they may be avoided by the use of colloidal silver preparations.

*Caution: The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria).*

### Colloidal Silver Preparations

In these, the silver does not exist to any great extent as free ions; therefore, it does not precipitate chlorides or proteins, and is noncorrosive and relatively or quite nonastringent and nonirritant, but a considerable degree of antiseptic action is retained. This is not proportional to the total silver content, and varies for the different compounds; suggesting that the antiseptic action is due to the liberation of very low concentrations of silver ions, which vary for the different compounds.

The mechanism of these effects is analogous to the late action of silver nitrate. This takes place in two stages: (1) the immediate irritant and germicidal effects produced by the direct application of the free silver ions; and (2) the later, milder antiseptic effects produced by the re-resolution of the protein silver compounds that were formed in the first stage. If the second stage alone is desired (i. e., mild antiseptics without irritation), the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation; for the absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be obtained by the resolution of the silver precipitates from silver nitrate. Since the direct application of the colloidal silver is less irritating, they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrheal infection evidently killing these organisms on direct contact Culver (*J Lab & Clin Med* 3 487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to 0.5 per cent mild protein silver or to 0.25 per cent strong protein silver. As regards other organisms discordant results have been reported.

Metallic silver and insoluble compounds of silver, such as the oxide, the halogen salts (iodide chloride etc.) and protein silver precipitates may be brought into colloidal solution, i. e., if they are sufficiently finely divided, they become miscible with water, so that they apparently go into solution (such 'colloidal solutions' are strictly permanent suspensions of the insoluble substance in a state of ultramicroscopic particles).

The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide or some protein silver precipitate in an excess of a denatured protein and drying *in vacuo*. This results in substances that dissolve very freely although somewhat slowly, in water yielding brown 'colloidal solutions' which contain so little of free silver ions that they do not readily precipitate chlorides or proteins. They consist of indefinite mixtures of metallic silver silver oxide and various silver protein compounds all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced. Although there are many gradations most of the products on the market fall into a small number of fairly definite therapeutic groups.

- (A) Protein Silver Strong Type
- (B) Protein Silver Mild Type
- (C) Collargol Type
- (D) Electric Type
- (E) Silver Halides

**A Protein Silver Strong Type**—Strong protein silver compounds contain the lowest percentage of silver (from 7.5 to 8.5 per cent) but have the strongest germicidal action and are distinctly irritant. They are therefore therapeutically intermediate between silver nitrate and mild protein silver. Protargol belongs to this group.

Protargol is said to be prepared by precipitating a 'peptone' (albumose) solution with silver nitrate or with moist silver oxide, dissolving the silver peptonate in an excess of protalbumose and drying *in vacuo* (Fraenkel).

**B Protein Silver Mild Type**—Mild protein silver compounds contain from 19 to 25 per cent of silver but are quite non-irritant. The following products listed in N. N. R. belong to this group: argyn, cargentos, silvol, solargentum. Squibb Argyn is defined as a colloidal compound of silver oxide and

serum albumin Solargentum-Squibb is prepared from alkali-gelatin, used as a solvent for silver oxide. The solution is then concentrated and dried *in vacuo*. Cargentos is prepared by suspending moist silver oxide in a solution of casein, and heating the mixture until no precipitate is obtained on the addition of solution of sodium chloride, and by evaporating the mixture to dryness in an air oven.

C. Collargol Type.—This contains a much higher percentage (78) of silver, said to be in the form of metallic silver, reduced to the colloidal form by chemical means, and "stabilized" by "a small percentage of egg albumin with products of oxidation." However, the albumin is denatured, since it does not precipitate on boiling; and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol, therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal-metal and oxide, and a smaller proportion in the form of proteinate. Its for intravenous results of Bott-  
ner (München 15] 1921) the  
therapeutic resp to the foreign  
proteins, rather than to the silver.

D. Electric Type.—Metallic silver may be brought into colloidal solution electrically, i. e., by forming an arc between silver electrodes under water. These solutions are very dilute and are not sufficiently stable for concentration. They are also likely to contain silver oxide, and sometimes ionized silver.

E. Silver Halides—These are mixtures of the colloidal silver salts (ten per cent of silver chloride in Lunosol; 18 to 22 per cent of silver iodide in Neo-Silvol) with suitable diluents. They are not astringent nor irritant, and are used as mild local antiseptics. They have the advantage of being colorless.

*Actions and Uses.*—The colloidal silver compounds are used mainly on mucous membranes, for antiseptics. The strong protein silver group is most effective in this respect, but is slightly irritant and stimulant. The mild protein silver group acts largely as mucilaginous demulcent and protective; and as detergent, by dislodging pus. Collargol acts locally like the protein silver, mild group, but is used mainly to produce systemic reactions.

The antiseptic efficiency of the silver compounds and their content of silver ions may be conveniently compared by their restraining effect on gas-formation by yeast, according to the method of Dreser, as modified by Pilcher and Sollmann (*J. Lab. & Clin. Med.* 8:301, 1923). According to this, the following solutions approximately equal the efficiency of a 1 in 1,000 solution of silver nitrate in the same media (*J. Lab. & Clin. Med.* 9:260, 1924) protargol in water 1 per cent, in physiological solution of sodium chloride 0.125, per cent, in

blood 0.9 per cent, and silver in water 36 per cent in physiological solution of sodium chloride 1 per cent in blood 3 per cent

**Dosage**—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong protein silver, from 5 to 50 per cent for mild protein silver, and from 0.02 to 1 per cent for collargol. These are applied every two to four hours, if possible. Solutions should be recently prepared, and should be protected against light. Ointments and suppositories are used with the same concentrations as the aqueous solutions. Stains on linen are removed by 1 in 1,000 solution of mercuric chloride. The usual concentrations for special purposes are shown in the adjoining table.

Eye	Strong Protein Silver Per Cent	Mild Protein Silver Per Cent
Conjunctivitis simple purulent or gonorrheal	2 to 10	Solution 25 Ointment 10
Prophylaxis against ophthalmia neonatorum	2 to 10	25
Prophylaxis before ophthalmic operations (several days)		25 50
Corneal ulcers		Spray, 10 to 20 Swab 25 to 50
Nose and throat	0.5 to 10	1 to 10 solution or ointment
Wounds and ulcers		10 dusting powder
Gonorrhea		
Injections—prophylactic	2	10
Acute	1/4 to 1	3 to 10
Chronic	2 to 10	10 to 20
Urethral irrigation	1:2,000 to 1:1,000	1:1,000
Urethral suppositories	5 to 10	20 (0.13 Gm.)
Cystitis		20 to 50 (5 cc.) or 10 to 25 (30 cc.) left in the bladder
Gynecologic practice		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	2	
Ointments	5	
Suppositories	5	Suppositories 20 (0.13 Gm.)
Rectal administration		
Irrigation	0.1	0.1 to 1
Injection	2	10
Suppositories	5 to 10	20 (0.13 Gm.)
Radiography		2 (solargentum) 50 (cargentos)

Since the advent of the sulfonamide compounds the use of silver salts for the treatment of gonorrhea, cystitis, sinusitis and in gynecologic practice has decreased enormously. Moreover the physician using silver salts must constantly keep in mind the possibilities of later argyria.

*(Early Preventive) Treatment of Venereal Diseases.*—The ordinary routine consists in washing the parts thoroughly with soap and water, after which a 2 per cent strong protein silver solution is injected into the urethra and held there for five minutes. The glans is then innuded with 30 per cent mild mercurous chloride ointment for five minutes.

The efficacy has been marked if the treatment is applied thoroughly within an hour after exposure, and is fair up to three hours. In the A. E. F. of World War 1, the ratio of diseases to exposure was about 1 in 30 without prophylactic treatment, and 1 in 90 with treatment. Prophylaxis, therefore, reduced the incidence to about one third (Ashburn, 1919). It is practically useless after five hours.

**LUNOSOL (Liquid).**—A preparation of colloidal silver chloride containing in 100 cc. silver chloride about 10 Gm, suerose about 84.5 Gm, sodium chloride about 1 Gm, and water about 47.8 Gm.

*Actions and Uses.*—Lunosol liquid has antiseptic and germicidal properties. It causes neither irritation of the mucous membranes nor coagulation of albumin even in concentrated solutions; it does not stain the skin on topical application. Possibilities of argyria from its continued use must constantly be kept in mind.

Lunosol liquid is intended for prophylaxis against and treatment of infections of the accessible mucous membranes, such as the genito-urinary tract and the eye, ear, nose and throat.

*Dosage.*—Lunosol liquid is generally used in solutions (colloidal suspensions) of from 1 to 25 per cent. In the male urethra, from 3 to 25 per cent solutions are used; for irrigation of the vagina, a 1 per cent solution is used, and on tampons, a 10 per cent solution; for irrigation of the bladder, a 0.1 to 1 per cent solution, and for irrigation of the rectum, a 1 to 5 per cent solution is used; in ophthalmia neonatorum, 25 to 50 per cent solutions are applied; in pyelitis, 3 to 10 per cent solutions are injected into the kidney pelvis; for application to the nose, eye and ear, the average concentration is 10 per cent.

#### *Tests and Standards*—

Lunosol (Liquid) is a milkwhite syrup, odorless, having a sweet metallic taste.

If a solution of 0.5 cc. of Lunosol in 25 cc. of water is treated with 0.6 Gm of potassium iodide dissolved in a few cc of water, a yellow liquid is formed. If 0.5 cc. of Lunosol is dissolved in 25 cc. of water and 8 cc. of strong ammonia water is added, a clear, colorless solution results. If a solution of 0.5 cc. of Lunosol in 10 cc. of water is treated with 15 cc. of tenth normal sodium thiosulfate, a clear colorless solution results. Place a few drops of Lunosol solution (1 in 10) in the nostril; no sensation of irritation is produced. To about 2 cc. of fresh undiluted egg white, add 1 cc. of Lunosol solution (1 in 10); shake the mixture, then allow to stand for fifteen minutes and finally dilute with 15 cc. of water; no precipitate forms.

Dissolve approximately 0.5 cc. of Lunosol, accurately measured, in 25 cc. of water, add 8 cc. of stronger ammonia water followed by an excess of nitric acid. Collect, wash, dry and weigh the precipitate.

The weight of silver chloride found corresponds to a content of not less than 9.5 nor more than 10 per cent of silver chloride in the specimen taken

### HILLE LABORATORIES

**Liquid Lunosol.** An aqueous solution containing 100 Gm of lunosol in each 100 cc (1 cc of liquid lunosol is equivalent in silver chloride content to 1 Gm of lunosol) marketed in  $\frac{1}{2}$  and 2 ounce dropper bottles, accompanied by an empty dilution bottle, thus affording a convenient means of preparing the various dilutions which may be indicated, also in 1 ounce and 4 ounce bottles for dispensing

**Unguentum Lunosol, 10 per Cent** Lunosol liquid, 10 cc incorporated in 90 Gm of an unguent base composed of about 17 Gm of water, 55.5 Gm of anhydrous lanolin and 27 Gm of liquid petrolatum in each hundred grams

U S trademark 189 347

**MILD PROTEIN SILVER**—Mild Silver Protein—Mild Protargin—Silver rendered colloidal by the presence of, or combination with protein. It contains not less than 19 per cent and not more than 23 per cent of silver (Ag) "U S P"

*"Caution—Solutions of Mild Protein Silver should be freshly prepared and should be dispensed in amber colored bottles"*  
U S P

For description and standards see the U S Pharmacopeia under Argentinum Proteomicum Mite

**Actions Uses and Dosage**—See preceding article, Colloidal Silver Preparations. Possibilities of argyria from its continued use must constantly be kept in mind

### ABBOTT LABORATORIES

**Argyn (Powder)** bulk A colloidal compound of silver oxide and serum albumin

U S trademark 137 522

**Argyn Tablets** 0.39 Gm

### PARKE, DAVIS & COMPANY

**Silvol (Powder)** bulk A colloidal compound of silver with an alkaline protein

**Capsules Silvol** 0.39 Gm

**Silvol Bougies, 5 per Cent** Bougies weighing 0.81 Gm and containing silvol 5 per cent in a base compound of oil of theobroma, wool fat, white wax, acacia and glucose

**Silvol Ointment, 5 per Cent** Silvol 5 per cent, in a base composed of petrolatum, wool fat, benzoated lard and white wax

**Vaginal Suppositories Silvol, 5 per Cent** Suppositories weighing 8.45 Gm and containing silvol 5 per cent in a base composed of gelatin and glycerin

**SHARP & DOHME, INC.**

**Cargentos (Powder):** bulk. A colloidal compound of silver oxide and modified casein.

U. S. patent 1,043,646 (Nov. 5, 1912; expired).

**E. R. SQUIBB & SONS**

**Solargentum (Powder):** 30 Gm., 120 Gm. and 453 Gm. bottles. A colloidal compound of silver and gelatin.

U. S. trademark 328,686

**Tablets Solargentum:** 0.3 Gm.

**NEO-SILVOL.**—Colloidal silver iodide compound.—A compound of silver iodide with a soluble gelatin base, containing 18 to 22 per cent of silver iodide in colloidal form.

**Actions and Uses**—Neo-silvol, even in concentrated solutions, causes neither irritation of mucous membranes nor coagulation of albumin. It does not stain the skin on topical application. Possibilities of argyria from its continued use must constantly be kept in mind.

Neo-silvol is intended for prophylaxis against, and treatment of, infections of accessible mucous membranes, especially of the genito-urinary tract and of the eye, ear, nose and throat.

**Dosage**—In the treatment of acute inflammations of the mucous membranes solutions of neo-silvol as strong as 50 per cent may be used. In inflammatory infections of the ear, nose and throat, 5 to 40 per cent solutions are used; for irrigating sinuses 2 to 5 per cent; for inflammatory conditions of the eye and conjunctival infections a strength of 10 to 40 per cent; in acute anterior urethritis, as an abortive measure, 20 per cent; for posterior urethritis or in the routine treatment of anterior urethritis, 10 per cent; in the genito-urinary tract of the female, from 10 to 50 per cent, as urographic medium, 20 per cent.

Solutions of neo-silvol are prepared by adding the substance to the required amount of water (hot, for concentrations of 25 per cent or over) and agitating the mixture until solution occurs.

Solutions tend to precipitate gradually after standing longer than a week. Local anesthetics should not be added to solutions of neo-silvol.

**Tests and Standards**—

Neo silvol is prepared by heating freshly precipitated silver oxide with gelatin (which has been previously dissolved in a dilute alkaline solution) until the silver oxide has been reduced to a metallic silver in a colloidal state of subdivision. The solution is treated with iodine, which combines with the silver. The liquid is then evaporated to dryness *in vacuo*. The finished product contains from 1 to 3 per cent of combined iodine in excess of that required for combination with the silver.

Neo-silvol occurs as pale yellow granules. In concentration up to 50 per cent neo-silvol forms with water almost colorless, milky or opalescent solutions (*colloidal suspensions*). Neo-silvol is insoluble in fixed oils, but slowly soluble in glycerin. Solutions of neo-silvol are not precipitated in the cold by strong acids or sodium chloride.

If a solution of neo-silvol is treated with a solution of potassium hydroxide no precipitate of silver iodide is formed, if this solution is boiled for a few minutes, it darkens gradually, but no precipitate is formed unless it is allowed to stand for some time. If a solution of neo-silvol is treated with dilute hydrochloric acid silver iodide is not precipitated, if this mixture is now boiled, the silver iodide is gradually precipitated. Dilute solutions of neo-silvol do not discolor in sun light (*absence of silver chloride and silver bromide*).

Transfer about 1 Gm of . . . . .  
Erlenmeyer flask containing  
until "solution" is effected  
gently over a flame for ten  
cool to handle, filter through  
thick pad of asbestos. Weigh  
hydrochloric acid (0.3 per  
cent of silver iodide the . . . . .

#### PARKE, DAVIS & COMPANY

Neo-Silvol (*Granules*): bulk

U S patent 1,610,391 (Dec 14, 1926, expires 1943) U S trade mark 157,369

Capsules Neo-Silvol: 0.39 Gm

Neo-Silvol Ointment, 5 per Cent: Neo-silvol, 5 per cent, in a base composed of glycerin, benzoated lard, hydrous wool fat and petrolatum.

Neo-Silvol Vaginal Suppositories: Neo-silvol, 0.454 Gm in a base composed of gelatin, glycerin and water.

**STRONG PROTEIN SILVER.**—Strong Silver Protein—Strong Protargin—"Contains not less than 7.5 per cent and not more than 8.5 per cent of silver (Ag)." U. S. P.

"Caution—Solutions of Strong Protein Silver should be freshly prepared and should be dispensed in amber-colored bottles" U. S. P.

For description and standards see the U S Pharmacopeia under *Argentum Proteinum Forte*.

*Actions, Uses and Dosage*—See preceding article, *Colloidal Silver Preparations*. Solutions are best prepared by dusting the powder on the surface of cold water, and allowing it to dissolve without stirring or shaking. This requires about ten minutes. Solutions should be freshly prepared. Possibilities of argyria from its continued use must constantly be kept in mind.

MERCK & Co, INC.

Silver Protein Strong (*Powder*): bulk



## WINTHIROP CHEMICAL COMPANY, INC.

**Protargol (Powder):** bulk. A colloidal compound of silver-albumose.

U. S. trademark 30,882.

**Granules Protargol Compound:** Protargol,  $33\frac{1}{3}$  per cent, and urea,  $66\frac{2}{3}$  per cent, added to increase the solubility.

## Silver Salts

**SILVER LACTATE.**—*Argenti Lactas.*— $\text{Ag C}_2\text{H}_3\text{O}_2 + \text{H}_2\text{O}$ .—The silver salt of lactic acid.

**Actions and Uses.**—Silver lactate is used as an active antiseptic. It is irritating if applied in substance to wounds. Possibilities of argyria from its continued use must constantly be kept in mind.

**Dosage.**—From 1 in 100 to 1 in 2,000 solutions.

**Tests and Standards.**—

Silver lactate is prepared by dissolving freshly precipitated silver carbonate in solution of lactic acid by the aid of heat, and concentrating the solution until crystallization begins. The operation must be conducted in a darkened room.

Silver lactate occurs in the form of crystalline needles, granular masses or crystalline powder; it dissolves in about 15 parts of water. Silver lactate when heated leaves a residue of metallic silver, weighing 50.0 to 51.5 per cent. It is usually colored somewhat brown and gives with water a brownish or reddish solution. The salt must be protected from the light.

## MERCK &amp; Co., INC.

**Silver Lactate (Crystals):** bulk.

**SILVER NITRATE.**—"When powdered and dried to constant weight in the dark over sulfuric acid, contains not less than 99.8 per cent of  $\text{AgNO}_3$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Argenti Nitras*.

## ABBOTT LABORATORIES

**Ampoules Silver Nitrate Solution, 1 per Cent:** 0.5 cc. wax ampul

## ARZOL CHEMICAL COMPANY

**Silver Nitrate Applicators:** Silver nitrate, 75 per cent, and potassium nitrate, 25 per cent, fused to one end of 3 inch and 6 inch wooden sticks. Each applicator is to be used but once.

## THE WM. S. MERRELL Co.

**Ampoules Solution Silver Nitrate 1 per Cent:** 0.5 cc. wax ampoules

## PARKE, DAVIS &amp; COMPANY

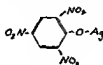
Capsules Solution Silver Nitrate, 1 per Cent 0.4 cc  
paraffin lined beeswax capsules

U S patent 1 527 659 (Feb 24 1925 expire 1)

## SHARP &amp; DOHME, INC

Ampoule Solution Silver Nitrate, 1 per Cent 0.2 cc  
beeswax ampul

**SILVER PICRATE**—Silver trimnitrophenolate —  $C_6H_3(OAg)(NO_2)_3 + H_2O$



**Actions and Uses**—Silver picrate has actions and uses similar to those of the other simple silver salts. Its crystals are available for treatment of glands by the aqueous solution.

The aqueous solution is used in the treatment of gonorrheal urethritis and the suppositories may be used in the treatment of gonorrheal vaginitis in children. It is also used in the form of a compound powder in the treatment of vaginitis due to *Trichomonas vaginalis* and *Monilia albicans*. This compound powder contains 1 per cent silver picrate in purified kaolin. It is administered by means of an insufflator or other surgical "powder blower". Another dosage form is intended primarily to be used as an adjunct in the treatment of this condition—vaginal suppositories containing 0.13 Gm in a boroglyceride gelatin base. Protracted use of this compound over a long period may possibly give rise to argyria because of its silver content and nephritis because of its picric acid content. It is therefore necessary to watch the skin for signs of argyria and the urine for albumin and casts. Possibilities of argyria from its continued use must constantly be kept in mind.

**Dosage**—Dilutions of from 1 to 2 per cent are used in the form of solution compound powder and vaginal suppositories.

**Tests and Standards**—

Silver picrate occurs as yellow crystals, slowly discoloring in sunlight. It is not soluble in acetone and alcohol.

Dissolve in	nitric acid	shake (thor-)	excess of a	ammonia w
Dissolve	about 150			

wash with water using about 300 cc. and ignite; the weight of ash on ignition does not exceed 0.5 per cent. To the foregoing filtrate, add 2 cc. of nitric acid followed by the addition of 5 cc. of dilute hydrochloric acid in small quantities with constant stirring, boil, allow to cool, collecting the precipitate of silver chloride on a Gooch crucible, wash with a diluted nitric acid and water, followed by the addition of a small quantity of alcohol and ether; finally dry to constant weight at 120 C.; the amount of silver calculated from the silver chloride found corresponds to not less than 30 per cent, nor more than 32 per cent.

**JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED**

**Silver Picrate Crystals: 2 Gm. bottle**

**Compound Silver Picrate Powder, 1 per Cent:** Silver picrate, 1 per cent, in purified kaolin

**Silver Picrate Jelly, 0.5 Per cent:** A water miscible jelly containing silver picrate, 0.5 per cent, in tragacanth jelly, 1.5 per cent.

**Silver Picrate Vaginal Suppositories: 65 mg. (infant size) and 0.13 Gm.** Silver picrate in a boroglyceride gelatin base.

**Soluble Trituration Silver Picrate, 20 per Cent, with Boric Acid, 80 per Cent:** A soluble mixture of silver picrate and boric acid.

### Peroxides

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide solution (*liquor hydrogenii peroxidi*) is official in the U. S. Pharmacopeia. This preparation is germicidal when diluted with not more than twice its volume of water. Diluted with an equal volume of water it destroys typhoid bacilli in two and one-half minutes.

Metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, and which are readily decomposed with liberation of hydrogen peroxide, or of oxygen.

*Actions and Uses* — Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of

the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited by the strong base formed when it dissolves in water.

Aqueous suspensions of zinc peroxide have been found useful in the local treatment of certain wound infections such as those caused by microaerophilic or anaerobic organisms, infections caused by some aerobes including hemolytic streptococci have also responded to such treatment.

Because of the strong oxidizing effects on the lower organisms, the peroxides have been recommended as a convenient means of sterilizing water.

**SODIUM PEROXIDE**—Sodium Peroxidum —  $\text{Na}_2\text{O}_2$ —The sodium compound analogous to hydrogen peroxide, containing at least 90 per cent of sodium peroxide.

*Actions and Uses*—Sodium peroxide is not used internally, but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

*Tests and Standards*—

Sodium peroxide occurs in the form of a white or yellowish, amorphous powder. It is soluble in water with decomposition and evolution of heat forming an alkaline solution and liberating oxygen. It dissolves in cold dilute acids, forming a solution of hydrogen peroxide. When heated sodium peroxide becomes darker, but on cooling resumes its original color. It does not react with alcohol, but it ignites ether on contact. A mixture with red phosphorus explodes under pressure on being struck. It is an extremely powerful oxidizing agent.

Sodium peroxide should not respond to tests for sulfates, chlorides, phosphates, nitrates and heavy metals. If 1 Gm. or 1.5 Gm. of sodium peroxide is weighed and gradually added with constant stirring to 950 cc. of diluted sulfuric acid (1 per cent) and the solution made up to 1,000 cc., the titration of 100 cc. of this solution with tenth normal potassium permanganate will indicate the presence of not less than 90 per cent sodium peroxide.

MERCK & Co., INC.

**Sodium Peroxide (Powder)**—bulk. Contains not less than 96 per cent of sodium peroxide.

**ZINC PEROXIDE MEDICINAL**—A mixture consisting essentially of zinc peroxide,  $\text{ZnO}_2$ , with varying amounts of zinc oxide,  $\text{ZnO}$ , and zinc hydroxide,  $\text{Zn(OH)}_2$ . The zinc peroxide content is not less than 45.5 per cent, equivalent to not less than 75 per cent of available oxygen.

*Actions and Uses*—See general article, Peroxides.

*Dosage*—Zinc peroxide medicinal (powder) sterilized in small quantities (10 to 50 Gm.) by heating in a dry oven for four hours at exactly 140 C. is made up with sterile distilled water to a smooth creamy suspension of about the consistency of heavy (40 per cent) cream. The dose depends entirely on the size of the wound to be treated. Enough of the creamy suspension should be used to provide the surface of the wound.

with a layer approximately  $\frac{1}{8}$  inch thick. If the suspension is too thin it runs off. If it is too thick it may not come in contact with all surfaces in the crevices of the wound. The suspension should be a cream and not a paste. The first layer, applied readily with a syringe, is then covered over with a thin layer of cotton soaked in the suspension and this in turn covered with a thick layer of cotton wet with water and then sealed with an impermeable covering or coating of some kind. Dressings are usually changed in twenty-four hours but may be left for several days.

### Tests and Standards.—

Zinc peroxide medicinal occurs as a fine, white, odorless, crystalline powder. It is insoluble in water but forms a smooth paste which does not cake or harden. A 5 per cent aqueous suspension of zinc peroxide medicinal separates to yield a clear supernatant liquid in thirty minutes, and bubbles of oxygen appear from the sediment.

Suspend 0.2 Gm of zinc peroxide medicinal in 10 cc. of water, add diluted hydrochloric acid dropwise until the bulk of the acid is dissolved and then add 1 cc. of sodium acetate solution. Filter the mixture and divide the filtrate into two portions. Boil one portion to remove peroxides and finally cool the solution responds to tests for zinc. Acidify the other portion with 1 cc of diluted sulfuric acid; the solution responds to tests for peroxides.

Transfer approximately 3 Gm of zinc peroxide medicinal to a beaker containing 50 cc of distilled water, add 20 cc. of diluted nitric acid and dilute to about 100 cc with distilled water. Add 25 cc of tenth normal silver nitrate, digest on the steam bath, filter and wash the precipitate with distilled water. Combine the filtrate and washings and titrate the mixture with tenth normal potassium thiocyanate to a faint brown color, using 3 cc of ferric ammonium sulfate solution as the indicator. Prepare and titrate a blank control; the difference between the volumes of thiocyanate solution observed in the two titrations is equivalent to a chloride content not greater than 1 per cent.

Transfer approximately 0.3 Gm of zinc peroxide medicinal, accurately weighed, to a 250 cc Erlenmeyer flask containing 50 cc. of diluted sulfuric acid. Shake the mixture until the powder dissolves and titrate the solution to a faint, permanent, pink color with tenth normal potassium permanganate.

	less than 45.5 per
	5 per cent (1 cc.
	to 4.869 mg. of

Cool the flask and contents to room temperature, mix the material well by shaking, allow to stand at least ten hours, mix again and use this heat-treated material for the following tests.

Transfer 5 Gm of the heat-treated material to a beaker, add 100 cc. of distilled water and shake thoroughly. After allowing the mixture to stand for fifteen minutes, determine the pH at 25 C. by means of a glass electrode. The pH is not less than 7.0 nor more than 8.5.

Transfer approximately 5 Gm of the heat-treated material, accurately weighed, to a 250 cc Erlenmeyer flask, add 100 cc. of distilled water at 37.5 C. and mix thoroughly. Submerge the flask and contents in a constant temperature water bath at 37.5 C. for two hours and finally filter through a fritted glass funnel. Wash the residue with 5 cc of distilled water, acidify the combined filtrate and washings with 20 cc of diluted sulfuric acid and titrate to a faint, permanent, pink color with tenth normal potassium permanganate, the active oxygen content is not less than 0.01 per cent (soluble peroxides).

Transfer 5 Gm of the heat-treated material to a dry 125 cc. Erlenmeyer flask, add 25 cc of distilled water at 37.5 C. and mix well. Fill the flask with distilled water at 37.5 C., shake thoroughly and

immediately insert a stopper equipped with a lead-over tube. The lead over tube should extend to within 1 cm. of the bottom of the flask and when inserted should be filled with liquid. Submerge the flask and contents in a constant temperature water bath at 37.5 C. and place a 25 cc. burette which has been filled to the lowest calibration mark with distilled water beneath the end of the lead-over tube. Measure the volume of liquid displaced after twenty four hours. The volume of liquid displaced is not less than 12 cc.

#### MALLINCKRODT CHEMICAL WORKS

Zinc Peroxide 45% ZnO Medicinal (Powder) 30 Gm  
113 Gm. and 453 Gm. bottles

#### MERCK & Co., Inc.

Zinc Peroxide-Special Medicinal (Powder) 30 Gm  
113 Gm. and 453 Gm. bottles

### Pyrethrum Preparations

**PYRETHRUM OINTMENT**—An ointment containing an extract from powdered pyrethrum flowers (*Chrysanthemum cinerariaefolium*). The extract is obtained by treating powdered pyrethrum flowers with a hydrocarbon oil of the kerosene type, this extract is then incorporated into an ointment base composed of hydrous wool fat, petrolatum and paraffin. The finished ointment contains 27 per cent of the active extract (representing 0.75 per cent of pyrethrins I and II) and 73 per cent of ointment base.

**Actions and Uses**—Pyrethrum ointment Upsher Smith has been shown to be an effective agent in the treatment of scabies. Based on the investigations of Sweitzer and Tedder (*Minnesota Medicine* 18:793 1935) and Sweitzer (*Journal Lancet* 56:467, 1936), the claim is made that the ointment penetrates the burrows and kills both the mites and the eggs and that except in rare instances it does not produce dermatitis with resultant exfoliation. Sweitzer and Tedder reported four cases of allergic sensitivity to the active substance in a series of 618 patients treated.

**Dosage**—The ointment is applied to the entire body following a thorough cleansing with soap and water. Further applications are made on at least three or four successive days. In most cases it is necessary to continue the treatment for a period of from five to seven days and in obstinate cases the use of the ointment may be required for a longer time. The ointment should not be used on patients who are sensitive to pyrethrum flowers.

#### Tests and Standards—

Pyrethrum ointment is an unctuous yellowish green mass.

Place 5 Gm. of pyrethrum ointment in a suitable flask, add 25 cc. of half normal potassium hydroxide alcoholic solution and an equal volume of water and heat the mixture under a reflux condenser for five minutes. The alcohol is removed by evaporation, the mixture cooled and allowed to separate. Remove the liquid by decantation, add

sufficient barium chloride solution, thoroughly mix and allow to separate. To the mixture add 1 cc. of sulfuric acid to remove the excess of barium salt. To about 5 cc. of the filtrate add an equal volume of mercuric sulfate solution; an immediate pink color develops which deepens on standing, finally changing to a green coloration with the development of a turbidity or a precipitate (monocarboxylic acid).

Determine the pyrethrin content by the procedure (with slight modification) described by Seil in "Soap" in May 1934; the combined pyrethrin content (pyrethrins I and II) is not less than 0.75 per cent nor more than 1 per cent.

#### UPSHER SMITH CO.

Pyrethrum Ointment: 100 Gm. and 600 Gm. containers

### Resorcin Compounds

**RESORCINOL MONOACETATE.**—Euresol—Resorcin Acetate, *m*-Hydroxyphenyl Acetate, —*m*-Acetyloxyphenol  $C_6H_4(OH).(OOCCH_3)$ . The monoacetic ester of resorcinol

**Actions and Uses.**—The action of resorcinol monoacetate is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol. Moreover, resorcinol monoacetate in contrast to resorcin does not give a greenish tint to light or gray hair.

Resorcinol monoacetate is used as an adjuvant in the treatment of acne, of sycosis vulgaris, of alopecia and of seborrhea.

**Dosage.**—Resorcinol monoacetate is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions, alcoholic solutions of from 3 to 5 per cent are used.

#### Tests and Standards.—

Resorcinol monoacetate is a viscous, lemon yellow liquid, boiling under ordinary pressure at 283 C. with decomposition. It is soluble in alcohol, acetone and most organic solvents; sparingly soluble in water. It has a faint characteristic odor and burning taste. Resorcinol monoacetate, at a pressure of 10 mm., distills completely between 150 and 153 C.

Dissolve 10 cc. resorcinol monoacetate in 20 cc. benzene and shake with 100 cc. of distilled water containing methyl orange solution; not more than 0.5 cc. tenth normal alkali is required to neutralize the free acidity.

#### BILHUBER-KNOLL CORP.

Euresol pro Capillis: Euresol perfumed to render it suitable for scalp lotions.

U. S. trademark 88,894

#### EASTMAN KODAK COMPANY

Resorcinol Monoacetate (Liquid): bulk

### Sulfoichthyolate Preparations and Substitutes

Preparations containing as their essential constituents salts or compounds of a mixture of acids containing sulfur and designated by the group name "sulfoichthyolic acid" are obtained

from certain bituminous shales. Sulfoichthyolic acid is characterized by a high sulfur content, the sulfur existing largely in the form of sulfonates, sulfones and sulfides. The ammonium compound of this so called sulfoichthyolic acid—first introduced as ichthyol—has been used most extensively. Compounds with sodium and other metals, with albumin, with formaldehyde, etc., have also been introduced.

A number of more or less related compounds of sulfur have been introduced as substitutes for the sulfoichthyolates, and the National Formulary contains a sulfoichthyolate preparation under the title "Ichthammol."

*Actions and Uses*—The current estimate of the effects of

internally, they produce some gastro intestinal irritation, with diarrhea, etc.

They were formerly used locally under the supposition that they secure the absorption of swellings and effusions in contusions, burns, etc., and especially in gynecologic practice, and in various skin diseases. They have been tried internally in a great variety of conditions, but there is no evidence that they are of any therapeutic value when used in this way.

**ICHTHAMMOL**—Ammonium Ichthosulfonate—'Ichthammol' is obtained by the destructive distillation of certain bituminous schists, sulfonating the distillate and neutralizing the product with ammonia. *N F*

For standards see the National Formulary under Ichthammol.

*Actions and Uses*—See general article, Sulfoichthyolate Preparations and Substitutes. Occasionally this compound is of definite value for local use in certain dermatologic conditions where a weak sulfur action is desired e. g., in Rosacea.

**CIBA PHARMACEUTICAL PRODUCTS, INC**

Isarol (*Liquid*): bulk Ichthammol

U S trademark 97 007

**HEYDEN CHEMICAL CORPORATION**

Ichthynat (*Liquid*): bulk Ichthammol

U S trademark 44 053

**MERCK & CO, INC**

Ichthyol (*Liquid*) bulk Ichthammol

U S trademark 275 443

**THIGENOL**—Solution of Sodium Sulfo Oleate—A solution of the sodium salts of synthetic sulfo oleic acids containing 2.85 per cent of sulfur.



**Actions and Uses**—See preceding article, Sulfoichthyolate Preparations and Substitutes.

**Tests and Standards.**—

Precipitated sulfur is dissolved by boiling in the glyceride of oleic acid; the resulting solution is treated with sulfuric acid, during which process sulfurous acid escapes, and a sulfo-oleic acid is separated out. The separated sulfo acid is then obtained by pouring into water and subsequently washing thoroughly. By treatment with solution of sodium hydroxide, there results a solution of sodium sulfo-oleate, which is evaporated in *vacuo* until it has a specific gravity of from 1.05 to 1.06.

Thigenol is a dark brown liquid, having a faint sulfurous odor. It is soluble in one or more parts of water, dilute alcohol, glycerin, chloroform, or oily or fatty bases, with any one of which it mixes freely. When water is the vehicle employed, it should be distilled, hard water will cause a precipitate.

Thigenol is incompatible with mineral acids or acetic acid

HOTTMANN-LA ROCHE, INC.

Thigenol (*Liquid*): bulk.

U. S. trademark 80,424.

## Ethylhydrocupreine

Ethylhydrocupreine is a synthetic derivative of cupreine,  $C_{10}H_{15}O_2N_2$ . Cupreine is an alkaloid occurring together with quinine in the bark of *Remyia pedunculata*. Ethylhydrocupreine may also be synthetically made from quinine. It is closely related to quinine, differing from the latter in containing two more hydrogen atoms and an ethoxy group in place of a methoxy group. Ethylhydrocupreine has the antimalarial and anesthetic action of quinine. Toxic symptoms, however, such as tinnitus, deafness, amblyopia or amaurosis (retinitis) are more liable to occur than with quinine. While these are generally transient, retinitis may result in permanent impairment of vision. This demand for a more powerful drug. Ethylhydrocupreine has a definite curative action on the pneumococcus in *vitro* and on the virulent strains of pneumococci. The internal treatment of lobar pneumonia in man has not been established. Ethylhydrocupreine hydrochloride has a definite value in the treatment of pneumococcic infections of the eye (ulcus corneae serpens).

## ETHYLHYDROCUPREINE HYDROCHLORIDE.—

N. F.—Optochin Hydrochloride—"Contains, when dried for 24 hours over sulfuric acid, not less than 90 per cent of ethylhydrocupreine base ( $C_{10}H_{15}O_2N_2$ )."  
N. F.

For description and standards see the National Formulary under Aethylhydrocupreinae Hydrochloridum.

**Actions and Uses**—See preceding article, Ethylhydrocupreine

**Dosage.**—For application to the eye and instillation into the conjunctival sac, a freshly prepared 1 or 2 per cent solution is used. It is not recommended for oral administration.

RARE CHEMICALS, INC.

Optochin Hydrochloride (*Powder*): bulk

Tablets Optochin Hydrochloride: 0.1 Gm

U S patent 1,062,203 (May 20, 1913, expired) U S trademark 343,326

## SYSTEMIC ANTI-INFECTIVES

### Antibacterial Agents

#### Chaulmoogra Derivatives

**CHAULMOOGRA OIL.**—Hydnocarpus Oil — "Chaulmoogra is the fixed oil expressed from the ripe seed of *Taraktogenes Kurzii* King, *Hydnocarpus Wightiana* Blume, or *Hydnocarpus anthelmintica* Pierre (Fam. Flacourtiaceae)." U. S. P.

For description and standards see the U S Pharmacopeia under Oleum Chaulmoograc.

In addition to small quantities of the glycerides of the fatty acids commonly found in vegetable fats, chaulmoogra oil contains the glycerides of a series of highly unsaturated fatty acids, chiefly chaulmoogric acid,  $C_{18}H_{30}O_2$ , and hydnocarpic acid,  $C_{18}H_{30}O_2$ . This series of fatty acids differs from other ordinary fatty acids in being optically active and in possessing, as part of the molecular structure, a ring of carbon atoms. Any therapeutic properties chaulmoogra oil may possess would appear to be due to these optically active unsaturated fatty acids of the chaulmoogric series.

Chaulmoogra oil has been used in the treatment of leprosy for many years, the evidence indicating that it is of possible value though not having specific, curative properties. Cases for treatment with this drug and its derivatives must be selected with great care or much harm may be done. Many experienced observers consider the oil and its derivatives valueless in the treatment of leprosy. Chaulmoogra oil is given by mouth or by hypodermic injection although the latter procedure is not devoid of disadvantages (abscesses).

The sodium salts of the fatty acids of chaulmoogra oil and the ethyl esters prepared from these fatty acids have been introduced for hypodermic use in the treatment of leprosy with the claim that they are better tolerated than the oil. In India preparations of the first kind have been used considerably and Leonard Rogers, in particular, reports the successful use of the sodium salts at first subcutaneously and later on intravenously. The ethyl esters prepared from the fatty acids of the oil have been used by several observers for a number of years.

**ETHYL CHAULMOOGRATE** — "The ethyl esters of the mixed acids of chaulmoogra oil." U. S. P.

For description and standards see the U S Pharmacopeia under Aethylis Chaulmoogras.

*Actions and Uses.*—See preceding article, Chaulmoogra Derivatives.

*Dosage.*—Orally, ethyl chaulmoograte is administered in gradually increasing doses of from 1 cc. to 5 cc. daily after meals with warm milk or hot tea. Intramuscularly, 1 cc. is the initial dose, this being increased by 1 cc. every second or third injection until a maximum of 3 cc. to 5 cc. is reached. The injections are administered once a week.

#### WINTHROP CHEMICAL COMPANY, INC.

Chaulmestrol (*Liquid*): bulk.

Ampules Chaulmestrol: 1 cc. and 3 cc.

U. S. patent 957,633 (May 10, 1910; expired). U. S. trademark 155,565.

#### Gold Compounds

**GOLD SODIUM THIOSULFATE.**—Sodii et Auri Thio-sulfas.—Sodium Gold Thiosulfate.—Sodium Aurothiosulfate,  $\text{Na}_2\text{Au}(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$ . The complex salt formed from 1 molecule of gold thiosulfate and 3 molecules of sodium thiosulfate. It contains approximately 37.4 per cent of gold.

*Actions and Uses.*—A review of the literature in regard to the use of gold and sodium thiosulfate in the treatment of lupus erythematosus reveals in general quite satisfactory clinical results, and it is considered a distinct advance in the therapy of this condition. Although there have been many recurrences in cases originally thought cured, nevertheless the beneficial and often curative action of the drug in a fair percentage of the cases seems to warrant giving it a definite place in the treatment of a disease for which at present there is no specific remedy.

Gold salts have also been recommended for use in the treatment of rheumatoid arthritis. The Council takes the viewpoint that until more convincing reports of their value have been presented, this therapy must be considered to be still in the experimental stage. This is particularly true in view of the high per cent of systemic reactions following their use.

Gold sodium thiosulfate must be used with extreme caution. This is especially true in the presence of tuberculosis and in diseases of the liver and kidneys. Dosages at first advocated have been found to be too great, resulting frequently in severe reactions, sometimes resulting fatally. Even with much smaller doses, accidents of this kind have occurred. The reactions most commonly encountered are varying degrees of fever, diarrhea, vomiting, albuminuria, enteritis, stomatitis, prostration and shock. Skin reactions consist of varying degrees of erythema, urticaria, severe papular and vesicular dermatitis, and scarlatiniform and exfoliative dermatitis. Cases of aplastic anemia, of hemorrhagic diathesis, and of agranulocytosis have also been noted following its use. Published necropsy reports

reveal conditions usually found in heavy metal poisoning. A certain number of cases of toxic hepatitis and of acute yellow atrophy have been noted after the use of this drug, likewise isolated cases of generalized pigmentations. Patients to whom gold salts are being administered should be warned of possible deleterious effects from strong sunlight. Moreover, they should not be given actinotherapy.

**Dosage** — At present the initial dose preferred is 5 mg intravenously or intramuscularly given in from 2 to 5 cc of sterile distilled water. Subsequent doses given at weekly intervals are increased 5 mg per dose, not exceeding a maximum of 50 mg for women and 75 mg for men, provided no reactions have occurred. The drug may be continued cautiously in smaller dosage following complete recovery from mild reactions but should be discontinued permanently if severe reactions have occurred. The liver should be examined at intervals of 2 to 3 weeks. If the liver is found to be diseased, the use of gold salts should be made with extreme caution. The use of gold salts should be made with extreme caution if the liver is found to be diseased. The use of gold salts should be made with extreme caution if the liver is found to be diseased.

Sodium gold thiosulfate occurs in white glistening needle-like or prismatic crystals. The aqueous solution is colorless. It is freely soluble in water, very slightly soluble in alcohol, ether and chloroform. An aqueous solution (1:200) is neutral or faintly alkaline to litmus. Sodium gold thiosulfate decomposes without melting when heated gently leaving a brown residue on ignition. An aqueous solution (1:200) assumes a yellow color on standing and decomposes.

Dissolve 0.1 Gm of sodium gold thiosulfate in 20 cc of water.

pounds)

Dissolve about 0.5 Gm of sodium gold thiosulfate accurately weighed in 5 cc of water carefully add 4.5 cc nitric acid and 25 cc

Transfer the filtrate from the gold precipitation to a 250 cc volumetric flask and make up to volume by addition of water. Pipet 50 cc of the solution to a 500 cc beaker add 5 cc hydrochloric acid

## ABBOTT LABORATORIES

Ampoules Gold Sodium Thiosulfate: 10 mg., 25 mg., 50 mg., 75 mg., 0.1 Gm., 0.25 Gm.

## THE LAKESIDE LABORATORIES, INC.

Ampoules Gold Sodium Thiosulfate: 10 mg., 25 mg., 50 mg. and 0.1 Gm.

## MERCK &amp; CO., INC.

Sealed Tubes Gold Sodium Thiosulfate: 10 mg., 25 mg., 50 mg., 0.10 Gm., 0.25 Gm., 0.50 Gm.

## G. D. SEARLE &amp; CO.

Ampuls Solution Gold Sodium Thiosulfate with Sodium Thiosulfate: 5 cc. containing gold sodium thiosulfate 50 mg. and sodium thiosulfate 0.75 Gm.

**TRIPHAL.**—A product consisting essentially of sodium aurothiobenzimidazole carboxylate,  $C_6H_4N:NHCsAu.COONa$ , with a small amount of a product of indefinite composition. The sodium salt of a compound formed by the interaction of gold halides with thiobenzimidazole carboxylic acid. Triphal contains from 44 to 47 per cent of gold.

**Actions and Uses.**—Proposed for use as a gold salt in the treatment of lupus erythematosus. Foci of infection, if present, should be removed before beginning treatment with triphal. It is contraindicated in pregnancy, kidney disease, acute progres-

its appearance triphal should be discontinued and intravenous injections of sodium thiosulfate instituted.

**Dosage.**—For adults, initial dose, intravenously, 5 mg., the dose being gradually increased to 75 mg.; for children, average initial dose, 0.5 mg., gradually increased, if possible, to 25 mg. once a week.

**Tests and Standards.**

— . . . . . colorless powder, readily soluble in . . . . . An aqueous solution of . . . . . stable for only a short time, . . . . . addition of mineral acids to . . . . . on addition of excess alkali solution.

Dissolve 0.1 Gm. triphal in 1 cc. water; a clear solution results. Transfer 1 cc. of triphal solution (1:200) to a clean test tube containing a freshly prepared solution of sodium stannite (prepared by



Dry about 0.1 Gm. of triphal, accurately weighed, for eight hours at 100 C. The loss in weight should not be more than 8.0 per cent nor less than 6.0 per cent of sample weight.

Transfer approximately 0.2 Gm. triphal, accurately weighed, into a tared porcelain crucible, and ignite well at red heat. Extract the residue with six 5 cc. portions of normal hydrochloric acid solution, filter each portion through an ashless filter paper. Transfer the remaining residue to the filter and wash with five 3 cc. portions of water. Transfer filter and residue to crucible, dry, and ignite to constant weight. The weight of the residue corresponds to not more than 50.0 per cent and not less than 47.8 per cent of gold, calculated to the dried basis.

#### WINTHROP CHEMICAL COMPANY, INC.

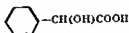
Ampules Triphal: 25 mg. and 0.1 Gm.

U. S. patent 1,558,584 (Oct. 27, 1925, expired)

U. S. trademark 188,475

#### Mandelic Acid Preparations

**MANDELIC ACID-U. S. P.**—Racemic Mandelic Acid—  
 "When dried over sulfuric acid for 18 hours, contains not less than 99 per cent of  $\text{HC}_8\text{H}_7\text{O}_3$ ." U. S. P. Mandelic acid has the following structural formula



For description and standards see the U. S. Pharmacopeia under Acidum Mandelicum.

**Actions and Uses**—Mandelic acid is a nonmetabolizable substance which when administered by mouth is excreted unchanged in the urine, and if the  $\text{pH}$  of the urine is kept at 5.5 or less it is rendered bactericidal or bacteriostatic against *Escherichia coli*, *Aerobacter* of the *Proteus* *Shigella* groups determinations of

reduced to  $\text{pH}$  5.5 or less, other acidifying agents such as

ammonium chloride, ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contraindications. For the same purpose the ketogenic diet has also been employed. Fluid intake should be restricted to an amount not exceeding 1,200 cc. daily. It is usually neither necessary nor advisable to continue mandelic acid therapy longer than from twelve to fourteen days, as renal irritation may ensue. Nausea, diarrhea, dysuria and hematuria may also occur occasionally, requiring reduction in dosage or interruption of therapy. Mandelic acid should not be administered in the presence of renal insufficiency, as an inadequate concentration is obtained in the urine; renal irritation may result, and serious acidosis may occur from retention of the acid.

*Dosage.*—The usual dosage is 3 Gm. four times a day either as the free acid or in the form of the sodium or ammonium salt. An additional acidifying agent is usually required when the sodium salt is employed.

**CALCO CHEMICAL DIVISION, AMERICAN CYANAMIDE COMPANY**

Mandelic Acid (*Powder*): bulk.

**GANE AND INGHAM, INC.**

Mandelic Acid (*Powder*): bulk

**MALLINCKRODT CHEMICAL WORKS**

Mandelic Acid (*Powder*): bulk.

**MERCK & CO., INC.**

Mandelic Acid (*Powder*): bulk

### *Mercuric Compounds*

**MERCURIC BENZOATE.**—Hydrargyri Benzoas.—Hydrargyrum Benzoicum— $\text{Hg}(\text{C}_6\text{H}_5\text{COO})_2 \cdot \text{H}_2\text{O}$ —The mercuric salt of benzoic acid

*Actions and Uses.*—Mercuric benzoate has been used for intramuscular injections in syphilis and locally in the treatment of gonorrhea but is largely replaced by organic mercury compounds

*Dosage.*—For intramuscular injection, mercuric benzoate is given in a 1 per cent solution by dissolving 0.3 Gm. of mercuric benzoate in 30 cc. of water, containing 1.5 Gm. of ammonium benzoate or given in 2 per cent solution with 2.5 per cent of sodium chloride, Gm or 0.03 Gm solution may be of sodium chloride

*Tests and Standards—*

Mercuric benzoate is a white, crystalline powder, slightly soluble in water, yielding a weakly acid solution, more soluble in an aqueous sodium chloride solution. It is insoluble in alcohol or ether. At 20 C a 10 per cent solution of sodium benzoate dissolves 1 per cent of its weight of mercuric benzoate. With alcohol mercuric benzoate is decomposed into a basic salt having a yellow color.

A solution of 1 Gm of mercuric benzoate and 0.5 Gm of sodium chloride in 20 cc of water yields a black precipitate with hydrogen sulfide, and with ferric chloride solution it yields a fawn-colored precipitate of ferric benzoate.

Shake 1 Gm of mercuric benzoate with 20 cc of water and filter. No turbidity is produced when silver nitrate solution is added to 10 cc of the filtrate acidified with a few drops of nitric acid (*chloride*). Two cc of a similar solution, when mixed with ferrous sulfate solution to which is added sulfuric acid so as to form a layer beneath, should produce no brown coloration at the zone of contact of the two solutions (*nitrate*).

Incinerate about 0.5 Gm of the salt in a porcelain crucible. Not more than 0.1 per cent of residue remains.

**MERCURIC**

Hydrargyrum— $\text{Hg}(\text{CN})_2$ ,  $\text{HgO}$ —  
containing from 5  
[ $\text{Hg}(\text{CN})_2$ ] and fr  
( $\text{HgO}$ )

*Actions and Uses*—Mercuric oxycyanide has been proposed as a substitute for mercuric chloride. Its antiseptic power is claimed to be greater and it is asserted to be less irritating than mercuric chloride because it does not act on albumin to the same extent. It has advantage over mercuric chloride in that it does not corrode steel instruments.

Representative syphilographers differ as to the use of mercuric oxycyanide intravenously. Some believe that its use should be limited to hospitals, others, that it has no advantage over others safe the  
loyed

by the intravenous route

*Dosage*—Mercuric oxycyanide may be administered in the same doses as mercuric chloride. It may be applied locally in solutions of 1 in 5000 or somewhat stronger.

*Tests and Standards—*

Mercuric oxycyanide occurs as a white or nearly white microcrystalline powder, soluble in about 80 parts of water, yielding a solution alkaline to litmus. Boiled with a mixture of sodium hydroxide, ferrous sulfate and ferric chloride solutions cooled and then treated with hydrochloric acid, mercuric oxycyanide yields a blue precipitate with ammonium chloride.

Tannic acid solution produces a tan colored precipitate. Both produce a black precipitate of mercuric oxycyanide. Potassium of mercuric oxycyanide yields



a red precipitate soluble in excess of the iodide. An aqueous solution should not respond to tests for chloride, nor should 0.2 Gm. leave a weighable residue when ignited.

Dissolve about 0.5 Gm. of mercury oxycyanide, accurately weighed, in 50 cc. of warm water, together with 0.5 Gm. of sodium chloride, cool the solution, add methyl orange and titrate with tenth-normal hydrochloric acid to the red end point. Add 2 Gm. of potassium iodide, dilute with water to about 150 cc. and titrate again with the tenth normal acid to the red end point; in the first titration, each cubic centimeter of tenth-normal hydrochloric acid solution is equivalent to 0.01083 Gm. of  $\text{HgO}$  and in the second, each cubic centimeter of tenth normal hydrochloric acid solution is equivalent to 0.012631 Gm. of  $\text{Hg}(\text{CN})_2$ .

#### ABBOTT LABORATORIES

Ampoule Solution Mercury Oxycyanide: 10 mg. in 5 cc.

#### ENDO PRODUCTS, INC.

Ampoule Solution Mercuric Oxycyanide: 8 mg. in 5 cc.

Ampoule Solution Mercuric Oxycyanide: 12 mg. in 5 cc.

#### THE LAKESIDE LABORATORIES, INC.

Ampule Solution Mercury Oxycyanide: 8 mg. in 5 cc

Ampule Solution Mercury Oxycyanide: 11 mg. in 5 cc

### *Methenamine Compounds*

**METHENAMINE.**—Hexamethylenamine—Hexamethylenetetramine.—“When dried over sulfuric acid for 4 hours, contains not less than 99 per cent of  $(\text{CH}_2)_6\text{N}_4$ .” U. S. P.

For description and standards see the U. S. Pharmacopeia under Methenamina and Tabellae Methenaminæ.

*Actions and Uses.*—Methenamine owes its action entirely to the liberation of formaldehyde, which occurs only in acid fluids. It is an active urinary antiseptic, provided the urine is secreted in an acid state. It has been shown that no antiseptic effects can occur in the body tissue and fluids which have a neutral or slightly alkaline reaction. Methenamine is not a uric acid solvent, and it has not given satisfactory results in gout. As a urinary antiseptic it is used less extensively, because there are other more effective agents.

Methenamine compounds simply possess the actions of methenamine and of the salts of the acid with which it may be combined.

Methenamine may produce urticaria on local application and, exceptionally, after internal administration. The liberation of formaldehyde in the bladder may cause vesical irritation.

#### MERCK & CO., INC.

Formin (*Powder*): bulk

U. S. trademark 152,230

#### THE WM. S. MERRELL COMPANY

Tablets Methenamine: 0.325 Gm. and 0.5 Gm.

## SCHEER &amp; GLATZ INC

Urotropin (*Crystals*) 33 Gm and 4.3 Gm bottles

Tablets Urotropin 0.3 Gm and 0.5 Gm

U. S. Trademark 269754

*Sulfonamide Compounds*

The group of compounds referred to as sulfonamides contain in common the chemical group  $-\text{SO}_2\text{N} <$ . The therapeutically active members of this group which have been accepted by the Council are derivatives of the sulfonamide called sulfanilamide and are characterized by the group  $\text{H}_2\text{N} \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{N} <$

*Actions and Uses*—The exact mode of action of the sulfonamide compounds on susceptible bacteria is still uncertain. Experimental evidence indicates that these compounds may interfere with the proper functioning of certain enzyme systems essential to the multiplication or survival of bacteria. Thus if a sulfonamide drug is present in the tissues in relatively low concentrations (as is generally true when these drugs are administered by the oral route) the rate of multiplication of susceptible bacteria is decreased (bacteriostatic effect) while if the drug is present in high concentrations (as occurs when local application of sulfonamide drugs is employed) an actual killing (bactericidal) effect may be noted on susceptible micro organisms.

In addition to this primary or direct effect of sulfonamide compounds on certain bacteria a secondary factor namely the host effect, may play a part in ridding the infected individual of invading bacteria. This has been especially studied in the instance of hemolytic streptococcus infections in which it has been demonstrated that the phagocytosis of streptococci noted in the course of sulfonamide therapy of streptococcal infections constitutes an important mechanism in bringing about the complete elimination of the infection. To what extent phagocytosis is important in other infections which are known to be susceptible to sulfonamide therapy has not as yet been established.

It has been demonstrated in the test tube that the addition of substances to culture mediums which act as growth factors for bacteria may decrease the bacteriostatic or bactericidal effects

a simple organic  
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possesses marked  
alizing relatively  
mpounds. This

observation is of especial importance when one considers that many local anesthetics (procaine is a good example) are esters

of para-aminobenzoic acid and hence break down in part to the parent substance when injected into the tissues. Pus and necrotic tissue have also been demonstrated to possess anti-sulfonamide properties. For this reason it is of importance to remove pus and necrotic tissue before sulfonamides are administered locally.

The choice of the sulfonamide compound which is to be used in the control of known infections should not be based on caprice or chance but on bacteriological diagnosis, experience dictated by knowledge of the experimental therapeutic background of these drugs, their pharmacologic properties in man, their clinical efficacy and finally, the variety, frequency and severity of the toxic reactions which may be produced by the drug.

When all these factors are taken into consideration, the following recommendations may be made at the present time concerning the selection of the proper drug for treating a given systemic infection: In hemolytic streptococcus infections due to Lancefield's Group A organisms, sulfadiazine is the drug of choice, with sulfanilamide second, sulfapyridine third and sulfathiazole fourth. Pneumococcal infections are best treated with sulfadiazine. Sulfathiazole is the second drug of choice in the . . . . . On the basis of existing . . . . . choice in the treatment of . . . . . is second, and the status of sulfadiazine in the therapy of such infections is in the stage of clinical investigation. *Sulfanilamide should never be used in the treatment of gonococcal infections unless the above mentioned sulfonamide drugs are unavailable.* Sulfadiazine or sulfathiazole is the drug of choice in the treatment of staphylococcal infections. Meningococcal infections respond well to therapy with sulfadiazine, sulfathiazole, sulfanilamide or sulfapyridine, but current evidence indicates that sulfadiazine is the drug of choice. Sulfadiazine is indicated for use in Friedländer's bacillus infections, with sulfapyridine second and sulfathiazole third. Recently a number of authors have proposed the oral administration of sulfadiazine for the treatment of gonococcal ophthalmia. It is believed that such use of sulfonamides shortens the period of active infection and diminishes the likelihood of ophthalmic complications.

The clinical evidence as to the effectiveness of sulfonamide compounds in the control of alpha-hemolytic streptococcus infections, is not completely clear. In tissue infections (other than subacute bacterial endocarditis) produced by the so-called "mouth varieties" of this organism, sulfanilamide, sulfadiazine, sulfathiazole and sulfapyridine seem to be about equally effective. None of the sulfonamides are active against the enterococcus group of streptococci. . . . . drug of choice in the treatment of . . . . . sulfonamides are effective . . . . . well to

sulfaguanidine, with sulfathiazole the second drug of choice. Sulfanilamide or sulfapyridine should on the basis of current evidence be used in the therapy of actinomycosis. In general urinary tract infections respond best to the sulfonamide drugs which are recommended for use in tissue infections produced by the same organism. *Anaerobic streptococcus* infections, regardless of their location, do not respond to sulfonamide therapy.

While reports of the definite clinical efficacy of the sulfonamide compounds are extant in respect to hemolytic streptococci Groups B and C, *Brucella melitensis*, *Pasteurella tularensis*, *Clostridium perfringens*, *Clostridium septicum*, *Hemophilus influenzae* and certain other bacterial infections, definite experimental and clinical data which would justify the selection of drugs of choice in infections caused by these organisms are not available at the present time, and the treatment of disease produced by these organisms with the sulfonamides must be regarded still as being problems of clinical investigation.

Four diseases of probable viral origin—trachoma, follicular conjunctivitis, lymphogranuloma venereum and molluscum contagiosum—respond to sulfonamide therapy. Clearcut data which permit one to judge the relative clinical efficiency of the various sulfonamide compounds in these infections are not available. The bulk of the clinical reports on these diseases deal with the therapeutic use of sulfanilamide or sulfapyridine. Further, while some cases of molluscum contagiosum no doubt respond to sulfonamide therapy, other less potent medicaments which may be applied locally offer equal therapeutic results.

Sulfadiazine has been demonstrated as an effective agent against the carriers of the meningococcus organism. Two grams a day for two days is usually adequate for treating carriers.

be evaluated. It appears quite certain that these compounds are ineffective in rheumatoid arthritis and are dangerous in the acute or active phase of rheumatic fever.

At the present time the Council feels that the evidence for the peroral prophylactic use of sulfonamides in rheumatic fever and for the prevention of pneumonia and other complications of common colds, influenza or measles is in the stage of clinical investigation, and their use should not be generally recommended.

Crystalline sulfonamides have been used extensively in the local treatment of certain bacterial infections. Present evidence indicates that crystalline sulfanilamide is highly effective as a topical agent in the therapy of superficial open hemolytic strepto-

coccus infections, while crystalline sulfathiazole is the drug of choice for the local therapy of staphylococcic infections. The incorporation of sulfonamides in ointment bases is still in the stage of clinical investigation; in the light of present information they should never be employed for a longer period than five days because of danger of sensitization of the patient. In the prophylaxis of contaminated wounds, crystalline sulfanilamide is the drug of choice. Crystalline sulfathiazole has been used, but in its present form, and owing to its lower solubility, it has a tendency to cake or crust in wounds, and when this occurs it may act as a foreign body. The use of solutions of sulfadiazine in triethanolamine in the prophylaxis of infection in and the treatment of burns is still in the stage of clinical

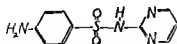
face of the wound, approximately 0.1 gram being used per square inch, but not over 10 grams per person for a 24 hour period.

**Determination of the Sulfonamides in Body Fluids.**—It is always desirable to determine the values for the sulfonamides in the blood and body fluids at frequent intervals by the method described by Bratton and Marshall (*J. Biol. Chem.* 128:537, [May] 1939).

Since the dosages suggested below are based on body weight in the metric system, the following table of approximations may be convenient for translating pounds into kilograms.

11 pounds = 5 kilograms	110 pounds = 50 kilograms
22 pounds = 10 kilograms	132 pounds = 60 kilograms
33 pounds = 15 kilograms	154 pounds = 70 kilograms
44 pounds = 20 kilograms	176 pounds = 80 kilograms
55 pounds = 25 kilograms	198 pounds = 90 kilograms
66 pounds = 30 kilograms	220 pounds = 100 kilograms
88 pounds = 40 kilograms	242 pounds = 110 kilograms

... -2-Sulf-sulfon-



**Clinical Pharmacology.**—Sulfadiazine resembles sulfapyridine in certain of its pharmacologic effects. When the drug is administered by the oral route its rate of absorption from the gastrointestinal tract is slower and, in general less complete than that of sulfathiazole or sulfanilamide. Sulfadiazine is, as a

rule, conjugated to the acetylated form in a lesser degree in the blood and tissues than is sulfanilamide, sulfathiazole or sulfapyridine. It does not pass into the body water as readily as does sulfathiazole or sulfanilamide, but it does pass into the cerebrospinal fluid in about the same manner as does sulfanilamide. The drug passes into pleural and abdominal fluids in concentrations of one half to four fifths of those noted in the blood and penetrates the red cells with ease.

It is excreted quite readily by the kidneys, in respect both to the drug itself and to its acetylated fraction. Relatively high concentrations of sulfadiazine are easily obtained in the blood of patients to whom the drug is administered, because it is not evenly distributed in the tissues of the body. If kidney function is impaired the excretion of sulfadiazine will be reduced and the drug will accumulate in the blood and tissues. The excretion of the drug is generally complete within forty-eight hours after the administration of a single dose of the compound and in the urine less sulfadiazine is found in the conjugated form than has been noted with sulfanilamide, sulfathiazole or sulfapyridine.

**Toxicity**—The toxic manifestations noted in the course of sulfadiazine therapy are similar to those noted previously in the course of therapy with the other sulfonamide drugs. They are generally unpredictable in their occurrence and are generally the result of an idiosyncrasy to the drug. Patients who are receiving sulfadiazine should be seen daily by their physicians in order that any possible toxic effects arising in the course of its administration may be noted and appropriate steps taken to eliminate the drug.

Sulfadiazine causes fewer toxic reactions than do sulfanilamide, sulfapyridine or sulfathiazole. Nausea, vomiting and dizziness are uncommon. Mental disturbances and psychoses have been described. Peripheral neuritis has not been reported.

Fever and rashes  
the other sulfon-  
receiving sulfadia-  
of the conjunctivas

and scleras has been noted. Hepatitis has not been reported, but leukopenia with granulocytopenia has been observed early and late in the course of the therapy. Acute agranulocytosis has been noted rarely occurring during the third week or later of therapy with this drug. Severe hemolytic anemias are rare. Microscopic and gross hematuria have been noted and oliguria and anuria with azotemia have been observed. It is probable that the mechanism responsible for these renal disturbances is the same as that which has been noted previously as producing such complications in the course of sulfapyridine or sulfathiazole therapy. It is important in the course of therapy to keep the urinary output at not less than 1000 cc daily. When fever, rash, hepatitis, granulocytopenia, acute hemolytic

anemia, agranulocytosis, hematuria with oliguria, anuria, injection of the scleras and conjunctivas or other serious toxic manifestations occur, the drug should be stopped and fluids forced in order that sulfadiazine may be eliminated from the body as rapidly as possible.

**Dosage.**—Sulfadiazine is poorly soluble and hence must be administered by the oral route. In adults suffering from pneumococcic pneumonia, severe hemolytic streptococcus infections, severe staphylococcic infections or meningococcic meningitis, the initial dose should be based on 0.10 Gm. per kilogram of body weight. Then, if the patient is suffering from pneumococcic pneumonia, 10 Gm. should be given every four hours day and night until the temperature has been normal for seventy-two hours. The drug may then be stopped. In severe streptococcic, staphylococcic and meningococcic infections, subsequent doses after the initial doses is 1.0 to 1.5 Gm. every four hours day and night until the temperature has been normal for from five to seven days. At this time the drug may be either stopped or continued in smaller doses until the complete recovery of the patient is assured.

In children suffering from pneumonia the initial oral dose should be based on 0.10 to 0.15 Gm. per kilogram of body weight, and subsequent doses should be one fourth of the initial dose given at intervals of six hours until the temperature has been normal for at least forty-eight hours. In severe streptococcic, staphylococcic or meningococcic infections in children the drug should be continued until five to seven days of normal temperature have elapsed. Then it may be discontinued or if considered necessary, continued in smaller doses until a cure is effected.

In mild or moderately severe hemolytic streptococcus infections, an initial oral dose of 0.05 Gm. per kilogram of body weight, followed by one-third of the initial dose given every four hours day and night by mouth until the temperature has been normal for three to five days, has been suggested as a satisfactory dosage schedule. All of the above dosages should be controlled if possible by determination of the concentration of the drug in the blood at frequent intervals (see Bratton and Marshall method under Actions and Uses above). In severe streptococcic, staphylococcic, meningococcic or Friedländer's bacillus infections it is necessary during the febrile period to obtain and maintain concentrations of approximately 15 mg. of sulfadiazine per hundred cubic centimeters in the blood of the patients. It is rarely necessary or advisable to attempt knowingly to exceed this concentration of the drug in the blood. In mild or moderately severe streptococcic infections, concentrations of the drug in the blood of 5 to 10 mg. per hundred cubic centimeters are usually satisfactory.

The incidence of oliguria, hematuria and anuria following sulfadiazine therapy may prove to be great under conditions

where the output of urine cannot be maintained above 600 or 800 cc. per day, as in tropical climates or where a shortage of water exists. It is recommended that under conditions where such complications are being encountered the medical officers shall administer an initial dose of 4 grams of sodium bicarbonate together with an initial dose of sulfadiazine, and shall follow this with 2 grams of sodium bicarbonate every four hours regardless of the dosage of sulfadiazine being employed. In the management of complications resulting from the toxic action of sulfadiazine on the kidneys, the administration of even larger doses of alkali such as 3 or 4 grams every four hours may be helpful.

### Tests and Standards—

Sulfadiazine occurs as a white odorless tasteless crystalline powder. It may be recrystallized from hot water to yield long flat needles which exhibit birefringence parallel extinction and a negative sign of elongation when viewed under a polarizing microscope. It is soluble in both alkaline and mineral acid solutions sparingly soluble in alcohol acetone and water (0.0123 Gm. per hundred cubic centimeters at 37° C.) insoluble in ether and chloroform. The melting point of sulfadiazine is 253-255° C. with decomposition.

Place about 0.5 Gm. of sulfadiazine in a test tube wrap the upper portion of the test tube with wet filter paper insert a thermometer and heat at 240-260° C. until a white crystalline sublimate forms in the neck of the tube. The melting point of the crystalline sublimate lies between 120 and 127° C. When recrystallized from hot benzene the purified 2-aminopyrimidine obtained melts sharply at 126-127° C. (distinction from other sulfanilamide derivatives). Under the polarizing microscope the sublimate appears as long acicular crystals exhibiting sharp parallel extinction. The fumes evolved during the decomposition do not discolor moistened lead acetate paper (distinction from sulfathiazole), no odor of ammonia is evolved and the residue is colored reddish brown (distinction from sulfanilamide and sulfaguanidine which evolve the odor of ammonia and leave a purple to violet residue).

Dissolve about 0.1 Gm. of sulfadiazine in about 0.5 cc. normal sodium hydroxide and dilute to 10 cc. with distilled water. Add 5 drops of copper sulfate; an olive green precipitate forms which will change to purple gray on standing (distinction from sulfapyridine which forms an apple green precipitate that turns olive green from sulfathiazole, which forms a violet precipitate from sulfaguanidine which forms a dark brown precipitate and from sulfanilamide which forms no precipitate or a light blue one).

Dissolve 0.5 Gm. of sulfadiazine in a mixture of 5 cc. of nitric acid and 5 cc. of distilled water and add 1 cc. of silver nitrate solution. Any turbidity produced is not greater than that formed in a control containing 0.1 cc. of fiftieth normal hydrochloric acid.

Dissolve 0.5 Gm. of sulfadiazine in 5 cc. of hydrochloric acid and 5 cc. of distilled water and add 1 cc. of barium chloride solution. Any turbidity produced is not greater than that formed in a control containing 0.1 cc. of fiftieth normal hydrochloric acid.

Dissolve 1 Gm. of sulfadiazine in 20 cc. of distilled water and add 10 per cent sodium hydroxide solution. The solution does not exceed 0.02 mg. of lead.

Dry an accurately weighed specimen of sulfadiazine to constant weight in vacuum over phosphorus pentoxide. The loss does not exceed 0.5 per cent.

The nitrogen content of dried sulfadiazine is not less than 22.1 per cent nor more than 27.5 per cent; the sulfur content is not less than 12.5 per cent nor more than 12.9 per cent.



Dissolve about 0.5 Gm of sulfadiazine in 10 cc. of distilled water and 10 cc. of concentrated hydrochloric acid contained in a 400 cc. beaker, dilute to 50 cc., cool to 15 C., and titrate with tenth molar sodium nitrite solution.

The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper (or clear glass plate). The solution should retain this endpoint for thirty seconds. Each cubic centimeter of tenth molar sodium nitrite corresponds to 0.02503 Gm. of anhydrous sulfadiazine; the amount of sulfadiazine found corresponds to not less than 99.5 per cent nor more than 101.0 per cent.

#### ABBOTT LABORATORIES

Sulfadiazine (*Powder*): bulk.

Tablets Sulfadiazine: 0.5 Gm.

#### LEDERLE LABORATORIES, INC.

Tablets Sulfadiazine: 0.5 Gm.

#### PARKE, DAVIS & Co.

Sulfadiazine (*Powder*): bulk.

Tablets Sulfadiazine: 0.5 Gm.

#### SHARP & DOHME, INC.

Tablets Sulfadiazine: 0.5 Gm.

#### E. R. SQUIBB & SONS

Sulfadiazine Powder (*Sterilized*): 5 Gm. vial.

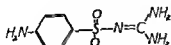
Tablets Sulfadiazine: 0.5 Gm

#### THE UPJOHN COMPANY

Tablets Sulfadiazine: 0.5 Gm.

**SULFAGUANIDINE**  $\text{C}_7\text{H}_{10}\text{O}_2\text{N}_4\text{S}$  Sulfaguanidine monohydrate monohydrate— $\text{C}_7\text{H}_{10}\text{O}_2\text{N}_4\text{S}$

Sulfaguanidine has the following structural formula:



**Clinical Pharmacology.**—The development of sulfaguanidine represented a new concept in bacterial chemotherapy, namely that a sulfonamide drug could be given by mouth and be quite soluble in the intestinal contents, while at the same time it would be poorly absorbed from the gastrointestinal tract, thus permitting the drug to exert its bacteriostatic and bactericidal action locally in the gastrointestinal tract.

The proper use of this drug demands that the physician shall use optimal doses spaced at such intervals as will give rise to

high concentration of the drug in the stool with possibilities for minimal absorption from the gastrointestinal tract. In actual practice, one finds that when the drug is properly administered the concentrations of sulfaguanidine in the blood rarely exceed 5 mg per hundred cubic centimeters.

On the basis of recent investigations the Council recognizes claims for the prophylactic use of sulfaguanidine as well as other sulfonamides in dysentery.

**Toxicity**—Sulfaguanidine is the least toxic of all commonly used sulfonamide drugs. Rare instances of nausea with vomiting, drug rash, drug fever and other types of idiosyncrasy have been reported. If toxic reactions occur, the drug should be stopped and fluids forced, and enemas given to eliminate the drug from the body as soon as possible.

**Dosage**—In bacillary dysentery the initial dose by mouth is 0.05 Gm per kilogram of body weight followed by a maintenance dose of 0.05 Gm per kilogram every four hours day and night until the number of stools is five or less daily, then 0.05 Gm per kilogram every eight hours for at least 3 days. If improvement does not occur within seven days it is unlikely that the drug will be effective on further administration. It is generally not considered wise to continue the drug for a period of more than fourteen days.

**Preoperative and Postoperative Use in Colonic Surgery**—When sulfaguanidine is being used as a prophylactic agent prior to operations on the colon, the recommended dosage is 0.05 Gm per kilogram of body weight by mouth every eight hours day and night for five days before the operation. Then as soon as possible after the operation, the drug should be started by mouth in the same dosage and continued for seven days. It is not, as a rule, necessary to continue the drug longer. It is recommended that the total period of dosage should not exceed fourteen days.

#### *Tests and Standards*—

Sulfaguanidine occurs as a white odorless crystalline powder. It may be recrystallized from hot water to yield long flat needles which exhibit birefringence, parallel extinction and a positive sign of elongation when viewed under a polarizing microscope. It is soluble in solutions of mineral acid, hot alcohol and in hot water (10 Gm. per 100 cc. at 100°C), sparingly soluble in ethyl acetate and insoluble in cold alkaline solutions, benzene, chloroform and ether. Sulfaguanidine exhibits a preliminary softening and melts between 182 and 192.5°C. In a short sealed tube sulfaguanidine melts between 141 and 145°C. Anhydrous sulfaguanidine melts between 190 and 192.5°C.

Place about 0.2 Gm of sulfaguanidine in a test tube and add 5 cc of 20 per cent sodium hydroxide solution. The sample does not dissolve. Heat the mixture to boiling; the solid dissolves and ammonia is evolved (distinction from sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine).

Dissolve 0.5 Gm of sulfaguanidine in a mixture of 5 cc. of nitric acid and 5 cc. of distilled water and add 1 cc. of silver nitrate solution. Any turbidity produced is not greater than that formed in a control containing 0.1 cc. of one fiftieth normal hydrochloric acid.

Dissolve 0.5 Gm. of sulfaguanidine in 5 cc. of hydrochloric acid and 5 cc. of distilled water and add 1 cc. of barium chloride solution. Any turbidity produced is not greater than that formed in a control containing 0.1 cc. of one-fiftieth normal sulfuric acid.

Ignite a weighed quantity of sulfaguanidine until it is thoroughly charred. Cool, add sufficient concentrated sulfuric acid to moisten the charred mass and ignite to constant weight: the residue is not more than 0.1 per cent.

Dissolve 1 Gm. of sulfaguanidine in 5 cc. of concentrated hydrochloric acid, dilute to 20 cc. with distilled water, and add 5 drops of freshly prepared 10 per cent sodium sulfide solution. The darkening produced does not exceed that developed in a control to which has been added 0.02 mg. of lead.

Dry an accurately weighed portion of sulfaguanidine to constant weight at 110 C. (or at 80 C. in vacuum over phosphorus pentoxide); the loss in weight is not less than 7.5 nor more than 8.0 per cent. The nitrogen content of the anhydrous sulfaguanidine obtained is not less than 25.9 nor more than 26.3 per cent; the sulfur content is not less than 14.8 nor more than 15.2 per cent.

Dissolve about 0.5 Gm. of sulfaguanidine accurately weighed, in 10 cc. of distilled water and 5 cc. of concentrated hydrochloric acid contained in a 400 cc. beaker, dilute to 50 cc., cool to 15 C., and titrate with tenth molar sodium nitrite solution. The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch iodide paste on white filter paper (or clear glass plate). The solution should retain this endpoint for thirty seconds. Each cubic centimeter of tenth molar sodium nitrite solution corresponds to 0.02142 Gm. of anhydrous sulfaguanidine; the amount of sulfaguanidine found corresponds to not less than 99.5 nor more than 101.0 per cent, calculated on the dried basis.

#### LEDERLE LABORATORIES, INC.

Sulfaguanidine (*Powder*): bulk.

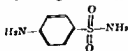
Tablets Sulfaguanidine: 0.5 Gm

#### E. R. Squibb & Sons

Sulfaguanidine (*Powder*): 120 Gm and 453 Gm bottles.

Tablets Sulfaguanidine: 0.5 Gm.

**SULFANILAMIDE.**—"When dried at 100° C. for 4 hours, contains not less than 99 per cent of  $C_6H_4O_2N_2S$ ." U. S. P. Sulfanilamide has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfanilamidum and Tabellae Sulfanilamidi.

**Clinical Pharmacology.**—Sulfanilamide when administered by mouth is readily absorbed from the gastrointestinal tract. It is probable that, following a single peroral dose, absorption is practically complete within four hours. The drug is evenly distributed in all body tissues with the exception of the brain, fat and bone. In patients with normal renal function, from 10 to 20 per cent of the circulating sulfanilamide is present in the acetylated or conjugated form. The drug is almost totally

absorbed and is readily excreted by the normal kidneys. In the urine ordinarily from one third to one half of the excreted sulfanilamide exists as the acetylated fraction.

**Toxicity.**—No patient should be treated with sulfanilamide unless arrangements are made for daily attention by a physician. This is necessary because of the serious toxic effects of this drug which while not frequent are generally unpredictable in their occurrence and probably result from an idiosyncrasy to sulfanilamide. Many patients receiving sulfanilamide will have signs and symptoms of central nervous system disturbances such as headache, dizziness, nausea, vomiting, mild depressions or elations and in a few instances severe toxic psychoses. Because of these toxic manifestations patients who are receiving the drug should be warned against driving automobiles, piloting or riding in airplanes and doing any heavy or dangerous work in which a spell of unconsciousness might result in an accident. Practically all doses of the drug develop a cyanosis apparent in the lips and on the entire integument. The exact mode of production of this cyanosis is unknown although in many instances it is due at least in part to the production of methemoglobin in the blood. It is not in the opinion of most observers a serious complication and rarely serves as an indication that treatment should be discontinued. Drug fever which commonly occurs between the fifth and ninth days of therapy is a not infrequent toxic manifestation. Rashes which may vary in their type and which may be accompanied by fever are also not infrequently seen in the course of sulfanilamide therapy. As these rashes are sometimes the result of a photosensitization of the skin it is probably best for patients who are receiving sulfanilamide to keep out of the sun and they should not receive ultraviolet irradiation.

Acidosis may be produced by the drug in certain individ-

anemia occurring from the first to the twenty first day of therapy is not uncommon and is noted more frequently in Negro patients than in white patients. A severe leukopenia may occur at any time during the course of therapy and granulocytopenia has been described not uncommonly as a toxic manifestation. The most common time for the appearance of true agranulocytosis is between the fourteenth and fortieth days of therapy. During this period white blood cell counts should be done at least every two days. In patients who have a decrease in renal function the normal excretion of the drug is impaired and

an accumulation of sulfanilamide in the blood and tissues of the patient may occur if care is not taken in regulating the dosage of the drug.

As far as is known, practically all other drugs may be prescribed concurrently (but not in combination) with sulfanilamide.

**Dosage.**—The dose of sulfanilamide depends on the type and severity of the infection. It is suggested that in cases of serious infection an initial peroral dose of 0.1 Gm. per kilogram of body weight be administered, this to be followed by doses of the drug of one-sixth the amount of the initial dose given at four hour intervals day and night until the temperature has been normal for seventy-two hours. Then the dose of the drug may be gradually decreased until complete convalescence is established. It is to be remembered that the main index for the control of therapy with this drug should not be the dose of the drug which has been prescribed but rather the concentrations of sulfanilamide that are being obtained in the blood or other tissue fluids. It is usually advisable to continue therapy for a few days after clinical recovery has taken place in order to avoid relapses. Patients who cannot take the drug by mouth may be given subcutaneous injections of a 1 per cent solution of sulfanilamide made up in isotonic solutions of sodium chloride or, better still, in one-sixth molar sodium racemic lactate solutions. The same total dosage may be employed for parenteral as for oral administration, but the injections should be given at intervals of from six to eight hours.

#### ABBOTT LABORATORIES

Ampoules Sulfanilamide (*Crystals*): 10 Gm. and 40 Gm.

Tablets Sulfanilamide: 0.324 Gm. and 0.5 Gm.

#### AMERICAN PHARMACEUTICAL CO., INC.

Sulfanilamide (*Powder*): 1 ounce, 4 ounce and 1 pound packages.

Tablets Sulfanilamide: 0.324 Gm. and 0.486 Gm.

#### GEORGE A. BREON & COMPANY, INC.

Sterators Sterile Sulfanilamide (*Crystals*): 5 Gm.

Tablets Sulfanilamide: 0.324 Gm.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Sulfanilamide: 0.5 Gm.

#### THE DRUG PRODUCTS CO., INC.

Pulvoids Sulfanilamide: 0.324 Gm.

#### ENDO PRODUCTS, INC.

Tablets Sulfanilamide: 0.324 Gm. and 0.5 Gm.

FLINT, EATON\* & COMPANY

Tablets Sulfanilamide 0.065 Gm 0.324 Gm and 0.5 Gm

GANE AND INGRAM, INC

Sulfanilamide (*Powder*) bulk

CHARLES C HASKELL & Co, INC

Tablets Sulfanilamide 0.324 Gm

HORTON & CONVERSE

Sulfanilamide Tablets 0.324 Gm

HYNSON, WESTCOTT & DUNNING INC

Sulfanilamide (Sterile Crystalline) 5 gram shaker type package

FEDERLE LABORATORIES, INC

Tablets Sulfanilamide 0.324 Gm

LEE LILLY AND COMPANY

Sulfanilamide (*Powder*) bulk

Pulvules Sulfanilamide 0.13 Gm and 0.324 Gm

MALINKRODT CHEMICAL WORKS

Sulfanilamide (*Powder*) bulk

THE MATTHE CHEMICAL COMPANY

Tablets Sulfanilamide 0.324 Gm

MCMEN LABORATORIES, INC

Tablets Sulfanilamide 0.162 Gm 0.324 Gm and 0.5 Gm

MERCK & Co, INC

Sulfanilamide (*Powder*) bulk

THE WM S MERRILL COMPANY

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

F S MILLER LABORATORIES, INC

Tablets Sulfanilamide 0.324 Gm

THE NATIONAL DRUG CO

Sulfanilamide (*Powder*) 453 Gm.

Tablets Sulfanilamide 0.065 Gm 0.324 Gm and 0.5 Gm

PARK, DAVIS & COMPANY

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

PITMAN MOORE CO

Tablets Sulfanilamide 0.324 Gm

**SCHIEFFELIN & Co.**

Tablets Sulfanilamide: 0.324 Gm. and 0.5 Gm

**SHARP & DOHME, INC.**

Tablets Sulfanilamide: 0.324 Gm and 0.5 Gm

**THE SMITH-DORSEY COMPANY**

Tablets Sulfanilamide: 0.162 Gm., 0.324 Gm and 0.5 Gm

**E. R. SQUIBB & SONS**Sulfanilamide (*Powder*): 120 Gm. and 453 Gm bottles.Ampul Sulfanilamide (*Crystals*): 1 Gm.

Tablets Sulfanilamide: 0.324 Gm and 0.5 Gm

**FREDERICK STEARNS & Co.**

Tablets Sulfanilamide: 0.3 Gm

**THE UPJOHN COMPANY**

Tablets Sulfanilamide: 0.065 Gm., 0.324 Gm and 0.5 Gm.

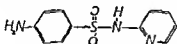
**THE WARREN-TEED PRODUCTS Co.**

Tablets Sulfanilamide: 0.33 Gm.

**JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED**

Tablets Sulfanilamide: 0.324 Gm., 0.5 Gm. and 0.65 Gm

**SULFAPYRIDINE**—"When dried at 100° C. for 4 hours, contains not less than 99 per cent of  $C_{11}H_{11}N_2O_2S$ ."  
U. S. P.



For description and standards see the U. S. Pharmacopeia under Sulfapyridinum and Tabellae Sulfapyridini.

**Clinical Pharmacology**—In comparison with sulfanilamide, sulfapyridine is irregularly and often poorly absorbed. These differences in absorption seem to be due to an individual response on the part of the patient. The drug is, as a rule, conjugated to the acetylated form in the blood and tissues in a higher degree than is sulfanilamide. These factors make it highly desirable that the concentrations of sulfapyridine be determined in the blood of patients who are receiving this drug, as irregularities in its absorption and conjugation may make treatment with it more difficult than when sulfanilamide is used. As far as is known, that fraction of the drug which is absorbed is excreted mainly by the kidneys in the free and conjugated forms. As a

rule, the drug is conjugated to the acetylated form in the urine to a higher degree than is sulfanilamide. Excretion of sulfapyridine is slower than is that of sulfanilamide, and it may be four or five days after the drug has been stopped before it is entirely eliminated from the body.

examination of the sputum obtained before drug treatment is begun) the etiologic agent which is causing the pneumonia, and if it is a pneumococcus, to type the organism in order that serum may be given if the pneumonia proves resistant to sulfapyridine therapy.

**Toxicity**—The toxic manifestations of sulfapyridine therapy are essentially those previously noted in the course of sulfanilamide therapy, and while, in general, the occurrence of toxic manifestations are not as frequent when sulfapyridine is used, they may be very severe. The toxic effects of this drug are unpredictable in their occurrence and presumably have as their basis an idiosyncrasy. Nausea and vomiting, sometimes very severe, are much more frequent in the course of sulfapyridine therapy.

The administration continued because of the treatment and or severe mental

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ment, and severe leukopenia or even granulocytopenia is not uncommon. It has been noted that children who are receiving sulfapyridine are more likely to develop a severe leukopenia than is the case when sulfanilamide is being given. Serious instances of hepatitis have been reported. Instances of gross hematuria with and without signs of renal failure have been noted in patients receiving this drug. It is likely that the hem-

manifestations of drug therapy arise, sulfapyridine should be stopped and fluids forced in order that it may be eliminated from the body as quickly as possible.

As far as is known sulfapyridine can be used concurrently with any other drugs.



*Dosage.*—In adults suffering from lobar pneumonia large initial doses such as 4 Gm. are given in a single dose followed by 1 Gm. of the drug every four hours by mouth, this to be continued until the temperature has been normal for at least seventy-two hours. Concentrations of 4 to 6 mg. of free sulfapyridine for each hundred cubic centimeters of blood seem to be necessary for prompt therapeutic responses to the drug. In infants and children the initial dose is 0.06 Gm. per pound up to 40 pounds (18 Kg.) of body weight; larger children require slightly less in proportion to their weight; hence a total of 40 grains (2.6 Gm.) is sufficient for a child weighing not more than 50 pounds (23 Kg.), a limit of not more than 3 Gm. to be given to any child weighing less than 60 pounds (27 Kg.). The total daily dose is calculated in the same manner, is divided into four parts and given at six hour intervals until the temperature has been normal for thirty-six hours. The drug may be stopped earlier in children than in adults without danger of relapse.

In the treatment of gonococcic infections in adults the following dosage schedule has been shown to give good results: the first day 3 Gm., then 2 Gm. a day for the succeeding nine days.

#### ABBOTT LABORATORIES

Capsules Sulfapyridine: 0.25 Gm.

Tablets Sulfapyridine: 0.5 Gm., plain and bisected

#### AMERICAN PHARMACEUTICAL CO., INC.

Tablets Sulfapyridine: 0.5 Gm.

#### CINA PHARMACEUTICAL PRODUCTS, INC.

Tablets Sulfapyridine: 0.5 Gm.

#### ENDO PRODUCTS, INC.

Tablets Sulfapyridine: 0.5 Gm.

#### FLINT, EATON & COMPANY

Tablets Sulfapyridine: 0.5 Gm.

#### LEDERLE LABORATORIES, INC.

Tablets Sulfapyridine: 0.5 Gm.

#### ELI LILLY AND COMPANY

Tablets Sulfapyridine: 0.065 Gm., 0.5 Gm. and 0.25 Gm.

#### MERCK & CO., INC.

Tablets Sulfapyridine: 0.5 Gm.

#### THE WM. S. MENNELL COMPANY

Tablets Sulfapyridine: 0.5 Gm.

## THE NATIONAL DRUG CO

Tablets Sulfapyridine 0.5 Gm

## PARKE DAVIS &amp; COMPANY

Capsules Sulfapyridine 0.25 Gm

Tablets Sulfapyridine 0.5 Gm

## PITMAN MOORE COMPANY

Tablets Sulfapyridine 0.5 Gm

## SHARP &amp; DOHME INC

Tablets Sulfapyridine 0.5 Gm

## THE SMITH DORSEY COMPANY

Tablets Sulfapyridine 0.5 Gm

## F. R. SQUIBB &amp; SONS

Sulfapyridine (Powder) 5 Gm vials

Capsules Sulfapyridine 0.25 Gm

Tablets Sulfapyridine 0.5 Gm

## FREDERICK STEARNS &amp; COMPANY

Tablets Sulfapyridine 0.5 Gm

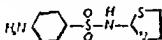
## THE UPJOHN COMPANY

Tablets Sulfapyridine 0.5 Gm

## JOHN WYETH &amp; BROTHER DIVISION WYETH INCORPORATION

Tablets Sulfapyridine 0.5 Gm

**SULFATHIAZOLE**—When dried at 100° C. for 4 hours contains not less than 99 per cent of  $C_{10}H_9N_3O_2S_2$ .  
 U. S. P.—Sulfathiazole has the following structural formula:



It may be prepared by the condensation of p-acetylamobenzenesulfonylchloride with 2-aminothiazole in pyridine. The compound 2-(p-acetylamobenzenesulfonamido)thiazole separates on dilution of the reaction mixture with water and is subsequently hydrolyzed with hydrochloric acid. Sulfathiazole is then isolated by neutralization of the acid solution to Congo red and purified by recrystallization from alcohol.

For description and standards see the U. S. Pharmacopeia and the U. S. National Formulary and Tables of Sulfathiazole.

*Clinical Pharmacology.*—Sulfathiazole resembles sulfanilamide in certain of its pharmacologic effects. In most patients it is rapidly absorbed when administered by mouth, maximum concentrations of the drug in the blood being obtained in three to six hours after the administration of a single dose. It is fairly evenly distributed throughout most of the body tissues with the exception that it does not pass readily into the spinal fluid. In the tissues a certain proportion of the drug is conjugated to the therapeutically inactive acetyl derivative. The degree of conjugation is, as a rule slightly greater than that noted for sulfanilamide but generally less than that for sulfapyridine. It is excreted rapidly by the kidneys, and because of this it is sometimes difficult to maintain adequate concentrations of the drug in the blood and tissues. The rapid excretion of this drug is probably responsible for its relatively low degree of conjugation. If kidney function is impaired, the excretion of sulfathiazole will be reduced and the drug will accumulate in the blood and tissues.

In the urine considerably less sulfathiazole is found in the conjugated form than has been generally noted for either sulfanilamide or sulfapyridine. The excretion of the drug is generally almost complete within twenty-four hours after the administration of a single dose of the compound.

Patients who are receiving this drug should be seen daily by their physicians in order that any possible toxic effects arising in the course of the administration of sulfathiazole may be noted and appropriate steps taken to eliminate the drug.

been noted. Sunburns, fever and drug rash than 10 pounds in common use. They occur between the fifth and ninth days of treatment but may occur at any period. Urticarial or nodular rashes resembling erythema nodosum are often seen. Patients receiving the drug should be kept out of the sun.

Hepatitis is rare. Leukopenia with granulocytopenia has been noted either early or late in the course of therapy. Acute agranulocytosis has been reported as occurring in course of therapy with this drug. Mild or severe acute hemolytic anemias are uncommonly seen. Microscopic or gross hematuria has occurred in patients who have received this drug, and anuria with azotemia has been observed. The hematuria and more

severe evidence of kidney damage may be due in certain instances to the formation of acetylsulfathiazole crystals and renal calculi which block the renal tubules or even the renal pelves and ureters but in other patients these toxic manifestations seem to result from a direct toxic reaction of the drug on the renal epithelium. Because of these renal toxic reactions it is important to keep the urinary output at not less than 1 000 cc in the course of therapy with sulfathiazole.

A curious toxic manifestation which has not been reported in the course of therapy with sulfamylamide or sulfapyridine and which has been noted frequently in the course of sulfathiazole therapy is the injection of the scleras and conjunctivas which when severe may give the appearance of the disease pink eye. Mild to severe arthralgia may accompany the fever and rashes which are produced by sulfathiazole.

When fever rash hepatitis granulocytopenia acute hemolytic anemia hematuria with oliguria injection of the scleras and conjunctivas or other serious toxic manifestations occur the drug should be stopped and fluids forced in order that sulfathiazole may be eliminated from the body as rapidly as possible.

As far as is known at the present time sulfathiazole can be used concurrently with any other drugs.

**Dosage**—Sulfathiazole is poorly soluble and hence must be administered by the oral route. In the treatment of pneumococcic pneumonia in adults the initial dose of sulfathiazole

1 Gm every four hours day

erature has been normal for

ould then be discontinued

pneumonia the initial dose

kilogram (up to 25 Kg of

body weight) and the total daily dose is calculated on the same basis. The total daily dose should be divided into four equal parts and administered at six hour intervals until the temperature has been normal for thirty six hours. The drug should then be stopped.

It is to be remembered that surgical measures both supportive and operative must be used in the treatment of staphylococcic infections in conjunction with sulfathiazole whenever indicated. Surgical drainage of purulent foci is generally advised because while the drug may halt the invasive manifestations of staphylococcic infection it may not by itself cure areas of localized infections and a flare up of the infection from such areas may occur if they are not properly drained.

The drug should not be used for the peroral treatment of minor staphylococcic infections such as localized boils and small carbuncles or any mild furunculosis. In large boils or carbuncles the initial dose for adults should be 4 Gm followed by 1 Gm every

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as long as evidence of a spreading infection continues. The dose should then be reduced to 1 Gm. every four hours day and night and continued as indicated. In staphylococcic bacteremia the initial dose for adults should be 4 Gm. followed by 1.5 Gm. every four hours day and night until the temperature has been normal for forty-eight hours. The dose may then be reduced to 1 Gm. to be given every four hours day and night for fourteen days, at which time the dose may be reduced to 0.5 Gm. every four hours day and night to be continued for a minimum of fourteen days. In severe staphylococcic infection in children the initial dose should be calculated on the basis of 0.2 Gm. per kilogram of body weight (up to 20 Kg. of weight). The total daily dose is calculated on the same basis and should be divided into six parts, given at four hour intervals day and night until the temperature has been normal for forty-eight hours. The dose may then be reduced to 1 Gm., to be given every four hours day and night for fourteen days, at which time the dose may be reduced to 0.5 Gm. every four hours day and night to be continued for a minimum of fourteen days. In staphylococcic bacteremia there is a great possibility that a relapse will occur unless prolonged treatment with the drug is employed. Sulfathiazole is at the present time the drug of choice in the treatment of gonorrhea. When used in this infection the first day's dose is 3 Gm., and 2 Gm. should be administered for the following nine days. If at the end of five days a pronounced improvement has not been noted, a shift should be made to either sulfapyridine or sulfadiazine.

It is very important to control the administration of sulfathiazole by determining its concentration in the blood of patients who are receiving it. In pneumonia, concentrations of from 4 to 6 mg. per hundred cubic centimeters of the drug in the blood should be sought.

#### ABBOTT LABORATORIES

Tablets Sulfathiazole: 0.25 Gm. and 0.5 Gm.

#### AMERICAN PHARMACEUTICAL CO., INC.

Tablets Sulfathiazole: 0.5 Gm.

#### GEORGE A. BREON & COMPANY, INC.

Sterators Sterile Sulfathiazole (*Crystals*): 5 Gm.

Tablets Sulfathiazole: 0.5 Gm.

#### BUFFINGTON'S, INC.

Tablets Sulfathiazole: 0.5 Gm. and 0.25 Gm.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

Sulfathiazole (*Powder*): 5 Gm bottle.

Sulfathiazole Tablets: 0.5 Gm.

DRUGS PRODUCTS COMPANY, INC

Pulvoids Sulfathiazole 0.5 Gm

ENDO PRODUCTS, INC

Tablets Sulfathiazole 0.5 Gm

FLINT, EATON & COMPANY

Tablets Sulfathiazole 0.5 Gm

THE LAKESIDE LABORATORIES, INC

Tablets Sulfathiazole 0.5 Gm

LEDERLE LABORATORIES INC

Tablets Sulfathiazole 0.5 Gm

ELI LILLY AND COMPANY

Sulfathiazole (*Powder*) Bulk

Tablets Sulfathiazole 65 mg 0.25 Gm and 0.5 Gm

MCNEIL LABORATORIES, INC

Tablets Sulfathiazole 0.5 Gm

THE MALTBE CHIMICAL COMPANY

Sulfathiazole (*Powder*) 30 Gm vial

Tablets Sulfathiazole 0.5 Gm

MERCK & Co, INC

Tablets Sulfathiazole 0.5 Gm

THE WM S MERRELL COMPANY

Tablets Sulfathiazole 0.5 Gm

F S MILLER LABORATORIES INC

Tablets Sulfathiazole 0.5 Gm

PARKE DAVIS & COMPANY

Tablets Sulfathiazole 0.25 Gm and 0.5 Gm

PITMAN MOORE COMPANY

Children's Tablets Sulfathiazole 0.25 Gm

Tablets Sulfathiazole 0.5 Gm

SCHIEFFELIN & Co

Tablets Sulfathiazole 0.5 Gm

SHARP & DOHME, INC

Tablets Sulfathiazole 0.25 Gm and 0.5 Gm

**THE SMITH-DORSEY COMPANY**

Tablets Sulfathiazole: 0.5 Gm.

**E. R. SQUIBB & SONS**Sulfathiazole (*Powder*): 5 Gm. vial.

Tablets Sulfathiazole: 0.5 Gm

**FREDERICK STEARNS & COMPANY**

Tablets Sulfathiazole: 0.5 Gm.

**THE UPJOHN COMPANY**

Tablets Sulfathiazole: 0.25 Gm. and 0.5 Gm.

**THE WARREN-TEED PRODUCTS CO.**

Tablets Sulfathiazole: 0.5 Gm

**WINTHROP CHEMICAL COMPANY, INC.**

Tablets Sulfathiazole: 0.25 Gm. and 0.5 Gm

**JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED**

Tablets Sulfathiazole: 0.5 Gm

373.4.

Succinylsulfathiazole possesses the following structural formula:



*Actions and Uses*—While succinylsulfathiazole has some resemblance to sulfathiazole, animal experiments show it to have low toxicity and to be poorly absorbed from the intestinal tract. Thus, it has been proposed for use as an intestinal bacteriostatic agent particularly with reference to gram negative organisms. Succinylsulfathiazole, while used in the intestinal tract for its local bacteriostatic effect, appears to differ from sulfaguanidine in toxicity—succinylsulfathiazole being less toxic. It has been proposed for use in preoperative preparation and postoperative treatment of patients requiring surgical procedure on the intestinal tract, such as operations for ulcerative carcinoma of the rectum, carcinoma of the colon, fecal fistulae, ileostomy, tumor of the cecum, etc. It is valuable in the treatment of acute bacillary dysentery and of carriers of dysentery bacilli.

**Dosage**—Preoperative, initially, 0.25 Gm per kilo of body weight by mouth, followed by a maintenance dose of 0.25 Gm. per kilo daily in six equal portions at four hour intervals. Postoperative 0.25 Gm per kilo daily for one or two weeks, depending on the postoperative condition. Postoperative administration should be begun as soon as the patient can take an ounce of water without undue nausea.

#### Tests and Standards—

powder  
filament  
us solu  
oroform  
100 cc  
succinyl  
sulfathiazole exhibits preliminary loss of water of hydration and melts between 190 and 195 C. In a short sealed tube succinylsulfathiazole melts over a range from 140 to 170 C.

Ignite a weighed quantity of succinylsulfathiazole until it is thoroughly charred. Cool, add sufficient concentrated sulfuric acid to moisten the charred mass and ignite to constant weight. The residue is not more than 0.1 per cent.

Dissolve 1 Gm of succinylsulfathiazole in 10 cc of normal sodium hydroxide. The solution is clear and colorless. Dilute to 20 cc with distilled water and add 5 drops of freshly prepared 10 per cent sodium

18.1 per cent

Dissolve about 0.5 Gm of succinylsulfathiazole accurately weighed in 10 cc of 20 per cent sodium hydroxide solution. Heat the mixture on a steam bath for two hours, cool, dilute to about 25 cc with distilled water, neutralize with hydrochloric acid and then add an excess of 5 cc. of hydrochloric acid. Cool the solution to below 15 C., and titrate with tenth molar sodium nitrite solution. The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch iodide paste on white filter paper (or clear glass plate). The solution should retain this endpoint for thirty seconds. Each cubic centimeter of tenth molar sodium nitrite



corresponds to 0.01734 Gm of succinylsulfathiazole: the amount of succinylsulfathiazole found corresponds to not less than 99.0 nor more than 101.0 per cent.

Dissolve 0.3 Gm. of succinylsulfathiazole in a mixture of 50 cc of alcohol and 50 cc. of distilled water, previously neutralized to phenolphthalein. Titrate the solution with tenth normal sodium hydroxide, using phenolphthalein as the indicator. Each cubic centimeter of tenth normal sodium hydroxide corresponds to 0.01867 Gm of succinylsulfathiazole: the amount of succinylsulfathiazole found corresponds to not less than 98.0 per cent nor more than 101.0 per cent.

### SHARP & DOHME, INC.

**Sulfasuxidine (Powder):** 115 Gm. and 450 Gm. glass jars

**Tablets Sulfasuxidine:** 0.5 Gm

U. S. patents 2,324,013 and 2,324,014 (July 13, 1943, expires 1960)  
U. S. trademark No. 394,111.

### *Sulfonamide Sodium Salts*

*Clinical Uses.*

When injected intravenously the sodium ions are promptly split off, leaving the sulfonamide compound in the circulating blood. Hence, in the final analysis, sulfonamide sodium salts represent vehicles for introducing the slightly soluble parent compounds into the body. The preferred method of administering the sodium salts of sulfonamide compounds is by the intravenous route as 5 per cent solutions in sterile distilled water. As there is a possibility that boiling or other methods of sterilization may result in the breakdown of the sodium salts, it is considered unwise and even unnecessary to attempt to sterilize 5 per cent solutions of these salts which are going to be used for intravenous therapy.

The administration of 5 per cent solutions of the sodium salts of the sulfonamide compounds by the intravenous route should be carried out carefully because these solutions, being highly alkaline, are definitely irritating to the tissues and, if they are permitted to leak outside the vein may cause necrosis of the tissues with sloughing. Solutions of such strength should never be given by the subcutaneous, intramuscular or intrathecal route because of the danger of producing a chemical necrosis of the tissues. Recently it has been shown that 0.3 to 0.7 per cent solutions of the sodium salts of the sulfonamide compounds can be safely administered in saline or isotonic solution of three chlorides by the subcutaneous route. However, the general use of this route is not advised unless the drugs cannot be administered by the intravenous route.

*Actions and Uses.*—The indications for the use of solutions of the sodium salts of sulfonamide compounds are those instances of severe infection in which it is desired to obtain promptly adequate blood concentrations of these drugs, or for patients who by reason of disturbances of the gastrointestinal tract, such as vomiting, are not obtaining proper concentrations of these

drugs when they are given orally and, finally, for patients in whom the absorption of these drugs is poor or their rate of conjugation is such that adequate concentrations cannot be obtained in the blood and tissues by other routes of administration.

With the exception of patients ill with severe infections, or those individuals to whom these drugs cannot be given by the oral route, it is rarely necessary to administer intravenous injections of solution of the sodium salts of the sulfonamides more than once or twice. Frequent and repeated injections of the drug are not generally advised, because such injections tend to produce thrombosis of the veins. Whenever possible, rather than continuing administration of solution of sodium salt of the sulfonamide compounds by the parenteral route, administration of the parent drug should be commenced by the oral route.

**Toxicity**—Aside from the damage to tissues which may result from the careless administration of the sodium salts of these sulfonamides by the intravenous route, the toxic reactions noted in the course of their administration are those which are noted when the parent sulfonamide is administered by the oral route.

**SULFADIAZINE SODIUM**—The sodium salt of 2 sulfanilamidopyrimidine— $C_{10}H_8N_4O_2S Na$  (M. W. 272.26)

**Actions and Uses**—The sodium salt of sulfadiazine has the same therapeutic activities and properties as does sulfadiazine. This compound has proved to be of value in the treatment of severe hemolytic streptococcus, pneumococcus, meningococcus, staphylococcus and *Escherichia coli* tissue infections.

**Dosage**—The usual initial dose of this drug for patients severely ill with pneumonia is based on 0.06 Gm. per kilogram of body weight, this being made up in a 5 per cent solution in sterile distilled water.

In severe staphylococcus, meningococcus or hemolytic streptococcus infections the initial dose should be 0.10 Gm. per kilogram of body weight.

For continuous therapy the drug should be administered by the intravenous route, but, if the patient is able to take the drug by the oral route, it is preferable to give the drug in this form. The dose of sulfadiazine sodium is 0.10 Gm. per kilogram of body weight, made up in a 5 per cent solution in distilled water and administered by the intravenous route at about twelve to fifteen hour intervals. When solutions of sulfadiazine sodium are being used as the sole means of therapy, daily determinations of the concentration of the drug in the blood should be made in order to prevent inordinately high levels of the drug from accumulating in the blood.

#### *Tests and Standards*—

Sulfadiazine sodium is a white odorless powder having a bitter taste. It is very soluble in water, soluble in alcohol and insoluble in

be isolated by appropriate methods. It is marketed in the form of anhydrous, monohydrated or sesquihydrated crystals.

Anhydrous sulfathiazole sodium has the following empirical formula:  $C_6H_4O_2N_2S_2Na$  (M. W. 277.3).

**Actions and Uses.**—The sodium salts of sulfathiazole have the same therapeutic activities as sulfathiazole. This compound has proved to be of value in the treatment of severe pneumococcic, meningococcic, staphylococcic and gonococcic infections.

**Dosage.**—The usual initial dose of the drug for patients severely ill with pneumonia is based on 0.06 Gm. per kilogram of body weight. Solutions of the drug should be prepared in the same manner as has been advised for solutions of sulfapyridine sodium, and the same precautions should be followed in respect to its administration.

### Tests and Standards—

Sulfathiazole sodium occurs as a white to faintly yellowish white, odorless, crystalline powder, possessing a bitter and saline taste. It is soluble in water, ethyl alcohol, methyl alcohol and acetone; slightly soluble in ethyl acetate and isopropyl alcohol; practically insoluble in benzene, carbon tetrachloride ether, and petroleum ether. Aqueous solutions of sulfathiazole sodium are alkaline to phenolphthalein; the pH of a 5 per cent aqueous solution lies between 9.5 and 10.0.

Dissolve 0.1 Gm. of sulfathiazole sodium in 20 cc. of water; the solution is clear and colorless. Divide the solution into two portions. Add to one portion 0.5 cc. of copper sulfate solution and stir; a grayish purple precipitate forms. Add diluted hydrochloric acid dropwise to the other portion until a precipitate forms, filter, wash the precipitate with water and dry it at 100 C.; the melting point of the crystals corresponds to that described for sulfathiazole; dip a clean platinum loop in the filtrate; the solution imparts an intense yellow color to a nonluminous flame.

Dissolve 0.5 Gm. of sulfathiazole sodium in 5 cc. of water, add 2 cc. of normal sodium hydroxide and boil gently; no ammonia is formed.

The amount of chloride ion must not exceed 0.01 per cent when determined according to the U. S. P. XII, page 626; the amount of sulfate ion must not exceed 0.02 per cent, when determined according to the U. S. P. XII, page 627; and the arsenic content after acid destruction of the original substance must not exceed five parts per million as arsenic trioxide when determined according to the U. S. P. XII, page 554.

Dissolve 0.5 Gm. of sulfathiazole sodium in 20 cc. of distilled water, add 5 drops of freshly prepared 10 per cent sodium sulfide solution; the darkening produced does not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dry about one gram of sulfathiazole sodium, accurately weighed, in a tared weighing bottle in constant weight in a partial vacuum at 100 C.; the loss in weight is not more than 9.0 per cent. Transfer about 0.5 Gm. of sulfathiazole sodium, accurately weighed, to a tared porcelain crucible; add 1 cc. of sulfuric acid and gently ignite the mixture. When fumes have ceased to arise, cool the crucible and add 0.5 cc. of nitric acid and 0.5 cc. of sulfuric acid and continue ignition to constant weight; the weight of the residue is not less than 24 per cent nor more than 26 per cent of the dried substance. Dissolve one gram of sulfathiazole sodium, accurately weighed, in 20 cc. of distilled water previously saturated with sulfathiazole at 25 C. Neutralize the solution with tenth normal sulfuric acid, using methyl red as the indicator. Allow the mixture to stand for one hour, filter by suction through a tared gooch crucible, wash the precipitate with small quantities of water previously saturated with sulfathiazole at 25 C., and finally

dry at 110 C for one hour the amount of sulfathiazole obtained is not less than 87.4 nor more than 92 per cent of the dried substance.

Dissolve about 0.5 Gm of sulfathiazole sodium accurately weighed in 50 cc of water and titrate with 0.02773 Gm of anhydrous sulfathiazole sodium found corresponds to not less than 99 nor more than 101 per cent of the dried substance.

MERCK & Co, INC

Sulfathiazole Sodium Sesquihydrate (*Powder*) 30 Gm, 113 Gm and 453 Gm

E R SQUIBB & SONS

Sulfathiazole Sodium Sesquihydrate (*Powder*) 5 Gm bottle

WINTHROP CHEMICAL COMPANY, INC

Sulfathiazole Sodium Anhydrous (*Powder*) 5 Gm bottle

Ampul Sulfathiazole Sodium, Anhydrous (*Powder*) 1 Gm

## Antiprotozoan Agents

### Antimony Compounds

**ANTIMONY THIOGLYCOLLAMIDE**—The triamide of antimony thioglycollic acid  $Sb(SCH_2CO NH_2)_3$ . It contains not less than 30 per cent of antimony.

**Actions and Uses**—Antimony thioglycollamide and antimony sodium thioglycollate are used in the treatment of granuloma venereum and are proposed for use in the treatment of lympho granuloma venereum and kala azar. These substances have been found to be less toxic and less irritating than antimony and potassium tartrate. The thioglycollamide has proved to be somewhat more toxic than the thioglycollate. The former is also less soluble but it has the advantage of being more stable. The drugs are used intramuscularly or intravenously.

**Dosage**—The usual intramuscular or intravenous dose employed by Randall is 0.08 Gm dissolved in 20 cc of sterile water every second day until from 15 to 25 injections have been given. He recommends that at least 12 injections be given after the first healing has taken place to insure permanent cure. Its solutions are incompatible with solutions of the fixed alkalis.

### Tests and Standards—

Antimony thioglycollamide is a white crystalline odorless powder. It is soluble in about 200 parts of water, somewhat soluble in alcohol and insoluble in ether. It melts at about 139 C. (uncorrected).

Dissolve a few crystals of antimony thioglycollamide in 5 cc. of water and add a drop of ferric chloride solution; a transient blue color appears. Heat about 0.1 Gm. of antimony thioglycollamide with 5 cc. of sodium hydroxide solution; ammonia is evolved. Dissolve about 0.1 Gm. of antimony thioglycollamide in 25 cc. of warm water, add a few drops of diluted hydrochloric acid and pass in hydrogen sulfide; an orange precipitate is produced.

Dissolve 0.2 Gm. of antimony thioglycollamide in 5 cc. of hydrochloric acid, add 10 cc. of freshly prepared stannous chloride solution and allow to stand 30 minutes; no brownish tint or precipitate is visible if viewed from above over a white surface (*arsenic*). A blank test should be carried out, using the same quantities of reagents.

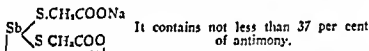
Weigh accurately from 0.2 to 0.3 Gm. of antimony thioglycollamide, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulfide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulfide, alcohol, ether, carbon disulfide, alcohol and ether, dry the residue at 110 C. and weigh. The antimony sulfide obtained corresponds to not less than 30 per cent of antimony.

HYNSON, WESTCOTT & DUNNING, INC.

Antimony Thioglycollamide (*Powder*): bulk.

Ampules Solution Antimony Thioglycollamide, 0.4 per Cent: 10 cc. and 20 cc.

**ANTIMONY SODIUM THIOGLYCOLLATE.**—The compound formed by dissolving antimony trioxide in a solution of a mixture of sodium thioglycollate and thioglycollic acid.



**Actions and Uses.**—The same as for antimony thioglycollamide. It is more soluble than antimony thioglycollamide, and in higher dosages it appears to be less toxic.

**Dosage.**—From 0.05 to 0.1 Gm. dissolved in 10 to 20 cc. of sterile water every third or fourth day until from 15 to 25 injections have been given. Its solutions are incompatible with solutions of the fixed alkalis.

**Tests and Standards.**—

Antimony sodium thioglycollate is a white or faintly pinkish powder; odorless or having a faint odor of mercaptan, very soluble in water; insoluble in alcohol.

Add a drop of diluted hydrochloric acid to 3 cc. of a dilute solution of antimony sodium thioglycollate (1 in 100) and add two drops of 1 per cent ferric chloride solution; a transient blue color results. Add a drop of 1 per cent ammonia water to this mixture and shake; a Burgundy red color results. Add a few drops of sodium hydroxide solution to dilute solution of antimony sodium thioglycollate (1 in 100); a white precipitate is produced. Dissolve about 0.1 Gm. of antimony sodium thioglycollate in 2 cc. of water, add a few drops of

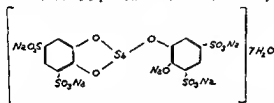
hydrochloric acid pass in hydrogen sulfide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulfide in a weighed Gooch crucible wash it successively with water containing hydrogen sulfide alcohol ether, carbon disulfide alcohol and ether dry the residue at 110 C and weigh. The antimony sulfide corresponds to not less than 37 per cent of antimony.

HYNSON, WESTCOTT & DUNNING, INC

Antimony Sodium Thioglycollate (Powder) bulk

Ampules Solution Antimony Sodium Thioglycollate  
0.5 per Cent 10 cc and 20 cc

FUADIN—Stibophen—Sodium Antimony III bis catechol 2,4 disulfonate  $[(NaO_2S)_2C_6H_3(O)_2SbOC_6H_3ONa(SO_3Na)_2] \cdot 7H_2O$ . It contains 13.6 per cent of trivalent antimony.



**Actions and Uses**—Fuadin is proposed for use in the treatment of granuloma venereum and of schistosomiasis (bilharziasis). Its action is reported to be more rapid and efficient in early granuloma venereum than in the later stages when there is scar formation. It is necessary to keep the treatment up for some time after all evidence of the disease has disappeared. In schistosomiasis it is indicated together with iron as the treatment of choice in the intestinal stage of the disease. The iron salts should be given after the completion of the treatment and not concurrently. The anemia, when present, is apparently due to a prolonged iron deficiency.

avenously), first day 1.5  
rd, fifth seventh ninth  
cc, a total of 40 cc of  
along in a week or two

weeks the course may be repeated and thereafter the drug is given once a week and then every fourteen days for several weeks to prevent relapse.

**Tests and Standards**—

Fuadin is supplied only in an approximately 63 per cent solution with not more than 0.125 per cent sodium bisulfite as a preservative. The solution is clear, odorless and nearly colorless; it possesses a slightly saline taste and acquires a faint pink color on standing in the light.

drop of the solution add 1 cc. of distilled water and one drop of mercurous nitrate solution: a black precipitate appears.

To 1 cc. of fuadin solution, add 2 cc. of a solution of magnesium uranyl acetate: a yellow crystalline precipitate appears. To 1 cc. of the solution add 2 drops of diluted nitric acid and 2 drops of silver nitrate solution: no opalescence is produced immediately (*chloride*).

To 2 cc. of fuadin solution add 20 cc. of bromine water and 1 cc. of diluted hydrochloric acid; expel the bromine by boiling and add 1 cc. of ammonium thiocyanate solution: no red color appears (*iron*). To 2 cc. of fuadin solution add 1 cc. of ammonium hydroxide and 2 drops of ammonium oxalate solution: no precipitate appears (*calcium*).

To 2 cc. of fuadin solution in a glass stoppered flask, add 2 cc. of diluted acetic acid and allow to stand five minutes.

after five minutes, sulfate, using a 1 per cent antimony content is not more than 0.05 Gm. per hundred cubic centimeters.

Transfer 5 cc. of fuadin solution to a 250 cc. beaker and add 18 cc. of diluted hydrochloric acid and 32 cc. of water. Evaporate the solution to about 5 cc. and neutralize with sodium hydroxide solution. Transfer to a nickel crucible, evaporate to dryness and add 3 Gm. of sodium hydroxide containing 5 per cent potassium nitrate. Fuse the mixture and heat until it is free from organic matter and dissolve the cooled melt in 100 cc. of water. Add by dilution with water.

chloride acid, add 1 Gm. sulfates by adding 5 cc. Digest on a steam bath in a crucible, ignite and weigh not more than 0.950 Gm. p

## WINTHROP CHEMICAL COMPANY, INC.

Ampoules Solution Fuadin: 3.5 cc. and 5 cc. Each 1 cc. contains fuadin, 0.064 Gm.; sodium bisulfite, not more than 0.125 per cent.

U. S. patents 1,549,154 (Aug. 11, 1925; expired) and 1,873,668 (Aug. 23, 1932; expires 1949). U. S. Trademark 304,950

## Arsenic Compounds

In some of the compounds listed in this chapter, the arsenic is pentavalent; in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic, their arsenic must be reduced to the trivalent form; this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases, the desirable, as well as the undesirable, effects produced by these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects may be due, at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites. In this way they become available for combating trypanosomiasis, treponematoses, spirillosis and other protozoan infections.

Among the advantages claimed for, or known to be possessed by, these compounds the following may be mentioned. In those known to produce their effects through the liberation of arsenic, the arsenic is liberated slowly, some remain in the circulating blood for a much longer period than do inorganic arsenic compounds and thus remain longer in contact with parasites which it is desired to kill, some are specifically ectotropic, that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Arsphenamine and analogous preparations of arsenic used intravenously come under the federal law covering serums, viruses, toxins and analogous products, and are subject to the same control.

#### COMPOUNDS CONTAINING TRIVALENT ARSENIC

According to Ehrlich's view, only trivalent arsenic is markedly toxic to spirochetes, trypanosomes, etc., hence he introduced a number of such compounds. Of these only the compounds in which the toxicity is reduced or modified by the introduction into the molecules of certain groups are listed below. These compounds have, according to Ehrlich, a special affinity for certain organisms, particularly spirochetes, while their toxicity for the higher animals is comparatively low. The exact fields of usefulness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. Undoubtedly some reactions are due to idiosyncrasies on the part of the patient. However, there is seen a large group of these cases which must be explained otherwise. Certainly, improper technique in the preparation of the drug as well as the improper (for example, too rapid) administration of the arsphenamines may add to the inherent toxicity. The administrator should always carefully observe the directions supplied by the manufacturers. If this be done and there are still reactions, then only should one look elsewhere for the causation.

The water used should be, if possible, freshly distilled and freshly sterilized. All chemicals should be pure. Any rubber tubing employed for the first time should be soaked over night in 5 per cent sodium hydroxide solution, then boiled in distilled water. Some reactions are due to the use of the same drug to a patient on a previous occasion. The drug should be prepared by previous use of arsenicals with a small dose—because of possible idiosyncrasies.

One should not be too much alarmed in a fresh case of syphilis by the reaction seen after the first injection of the arsphenamines—the Herxheimer reaction. It is that phenome-

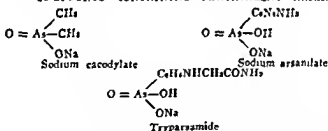


non of the reaction of the disease to the arsphenamine in which there is a rise of temperature, headache, possible nausea, malaise, and marked accentuation of the cutaneous and mucous membrane symptoms. One should be concerned, however, if with succeeding injections there are promptly recurring reactions in the form of gastritis, itching of the skin, urticaria, conjunctivitis, fixed areas of dermatitis that flare up with each new injection, and more or less generalized dermatitis or jaundice. In addition, there are sometimes noted generalized exfoliative dermatitis, purpura hemorrhagica, aplastic anemias, acute yellow atrophy and encephalitis.

The best treatment of these conditions is prophylaxis, and these drugs should never be readministered without inquiry of the patient and examination of the skin as to possible pruritus, jaundice, cutaneous eruptions, or other symptoms. Moreover, a urine examination should always be a preliminary.

Arsphenamines are contraindicated or should be used with special caution in diseases of the eye of a nonsyphilitic character, in severe affections of the heart and blood vessels, the lungs and the kidneys and in advanced degenerative processes in the central nervous system. They should also be used with caution in infants. Arsphenamine should not be used in beginning luetic optic neuritis until after some preliminary antiluetic therapy with either bismuth or mercury salts.

#### COMPOUNDS CONTAINING PENTAVALENT ARSENIC



In one of the compounds listed above, the arsenic is in combination with an alkyl group and is thus analogous to the cacodylates; in the others the arsenic is in combination with aniline, and is thus analogous to arsanilic acid.

Arsanilic acid is derived from arsenic acid,  $\text{AsO}_3(\text{OH})_2$ , by replacing one hydroxyl by aniline (phenylamine)  $\text{C}_6\text{H}_5\text{NH}_2$ ; related compounds are made by substituting derivatives of aniline.

The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

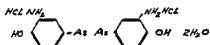
Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide which gives a foul odor to the breath per spiration etc. Further changes yield products containing inorganic trivalent arsenic by which the therapeutic effects if there are any are produced. It is not used in the treatment of syphilis.

Sodium arsanilate acts with especial violence on the optic nerve, producing optic atrophy frequently resulting in permanent blindness. This may occur unfortunately even with therapeutic doses. It is not used in the treatment of syphilis.

Tryparsamide is a powerful trypanocide and only slightly treponemacidal. The drug according to studies of Voegtlin and co workers when injected intravenously results in pronounced penetration of the nervous system tissue. This may explain its great value in the treatment of resistant syphilis of the central nervous system. It seems to be particularly valuable following malaria therapy. The suggestion has been made by Young and Loevenhart that the effect on the optic nerve frequently seen after tryparsamide is due to the presence of the amino group in the para position to the arsenic (Stokes). Because of this fact the physician should exercise great caution in the use of this drug.

### Compounds Containing Trivalent Arsenic

**ARSPHENAMINE** — Diaminodihydroxyarsenobenzene Dihydrochloride — Contains not less than 30 per cent and not more than 32 per cent of arsenic (As) and complies with the requirements of the National Institute of Health United States Public Health Service U S P



For description and standards see the U S Pharmacopeia under Arspenamina.

**Actions and Uses**—Arsphenamine is useful as a specific remedy for syphilis in all stages. According to available data in incipient tabes, early paralysis, epilepsy and cerebrospinal syphilis the drug can be employed with the prospect of most benefit in those cases in which its use is begun early.

The drug is used in the spirillum affections such as relapsing fever and frambesia.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system and cachexias unless these are a direct result of syphilis. It is also contraindicated in patients who have pronounced idiosyncrasy against arsenic.

It has been employed successfully in various types of syphilitic diseases of the eyes. As a rule in such cases it is well

to give a preliminary course of mercury or bismuth injections in order to obviate the danger of a Herxheimer reaction. Repeated injections should be given. It may be used up to 0.01 Gm. per kilogram of body weight, but it is better to keep under this dose.

*Dosage.*—Usually from 0.2 to 0.4 Gm.; though 0.6 Gm. may be given, the smaller doses are more extensively used.

For children from 0.1 to 0.2 Gm. In infants doses of from 0.02 to 0.1 Gm. may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is preferable and is to be recommended.

For intravenous injection one should proceed thus:

The ampul containing the drug is immersed in alcohol, in order to be sure that a cracked tube is not being used; then the tube is carefully wiped off, the neck filed across and broken off, and the contents sprinkled on sterile distilled water (10 cc. for each 0.1 gram of the drug used), contained in a sterile Erlenmeyer flask. The drug is allowed to dissolve with little or no agitation. Normal sodium hydroxide is then added to the solution, using 0.85 cc. to every 0.1 Gm. of the drug. Thus 0.6 Gm. of the drug would require 5.1 cc. of normal alkali. A precipitate of the base is first formed, which, after the contents are carefully agitated, is again brought into solution, the fluid being strongly alkaline. Filter the alkalized solution through sterile gauze, 4 ply, and dilute the filtrate with sterile distilled water to make 25 cc. for each 0.1 Gm. of the drug. It should stand 30 minutes before using. At least one minute should be allowed for each 25 cc. of the solution to flow into the vein, using the gravity method. The directions accompanying the drug as to temperature of the water, etc., should be followed. The contents of a tube should be mixed at once after opening, and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used. In all cases the skin should be disinfected with tincture of iodine or with alcohol.

#### ABBOTT LABORATORIES

Ampoules Arsphenamine: 0.3 Gm, 0.4 Gm, 0.6 Gm, 1.0 Gm, 2.0 Gm, and 3.0 Gm.

#### DIANSENOL COMPANY, INC.

Ampoules Diarsenol: 0.1 Gm, 0.2 Gm., 0.3 Gm, 0.4 Gm., 0.5 Gm., 0.6 Gm., 1.0 Gm, 2.0 Gm, and 3.0 Gm.

#### MALLINCKRODT CHEMICAL WORKS

Ampoules Arsphenamine: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm, 0.5 Gm, 0.6 Gm., 1.0 Gm, 2.0 Gm, and 3.0 Gm.

#### MERCK & CO., INC.

Ampoules Arsphenamine: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm, 0.5 Gm, 0.6 Gm, 1.0 Gm. and 3.0 Gm.

## WINTHROP CHEMICAL COMPANY, INC

Salvarsan (Powder): bulk Arsphenamine

Ampoules Salvarsan: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm  
0.5 Gm, 0.6 Gm, 1.0 Gm, 1.2 Gm, 2.0 Gm, and 3.0 Gm

BISMARSEN C. 1000 mg. — Rem. th. — Rem. th.

24 per cent of bismuth

**Actions and Uses**—For the treatment of syphilis. The drug is said to be somewhat slower in its action than intramuscularly administered sulfarsphenamine or intravenously administered neoarsphenamine. Some pain at the site of injection may be noted.

**Dosage**—Bismarsen is administered intramuscularly. The initial dose is 0.1 Gm. The dose is dissolved in 1 to 2 cc of a sterile solution of sodium sulfate. Weekly doses in courses of treatment of twenty doses, or more.

**Tests and Standards**—

Bismarsen is prepared by adding a solution of potassium bismuth tartrate in water to an aqueous solution of 3,3'-diamino-4,4'-dihydroxy-arsenobenzene N,N'-dimethylene sulfonate, dissolving the precipitate.

bismarsen the solution is at first turbid, then becomes a deep reddish brown with formation of a precipitate. Add 1 cc of mercuric potassium iodide solution to 5 cc of a 1 per cent solution of bismarsen the solution yields a greenish yellow opalescence, which in turn assumes a dirty green color on standing. Add drop by drop 2 cc of a 40 per cent sodium hydroxide solution to 5 cc. of a 1 per cent solution of bismarsen the solution gradually darkens without any formation of precipitate. Add 0.5 cc. of a 2 per cent silver nitrate solution to 5 cc. of a 1 per cent solution of bismarsen a dark red solution is produced (distinction from arsphenamine). Add 1 cc. of a saturated solution of bromine in water to 5 cc. of a 1 per cent solution of bismarsen. The solution yields a greenish brown precipitate (distinction from sulfarsphenamine, neoarsphenamine and arsphenamine). Add 0.5 Gm of zinc dust and 5 cc of diluted hydrochloric acid to 0.1 Gm. of bismarsen in a test tube and at the mouth of the tube hold a strip of filter paper moistened with 5 per cent cadmium chloride solution the paper turns yellow in four minutes.

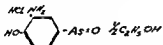
Transfer about 0.4 Gm. of bismarsen, accurately weighed, to a Kjeldahl flask, add 2 cc. of sulfuric acid and heat carefully; add 2 cc. of nitric acid a drop at a time, continue heating until brown fumes cease to be given off, cool and add water to make 120 cc.; if a white crystalline precipitate appears, dissolve it with a few drops of hydrochloric acid; transfer to a 250 cc. beaker, add 7 Gm. of tartaric acid, neutralize with strong ammonia water and add 10 cc. of magnesia mixture followed by 20 cc. of stronger ammonia water, allow to stand twelve hours, filter through a hard surface filter paper and wash the precipitate with 50 cc. of 2.5 per cent ammonia water, puncture the filter, transfer the precipitate into a 250 cc. beaker with washings, then add just sufficient hydrochloric acid to dissolve the precipitate, filter, wash the filter well with water, neutralize the filtrate with stronger ammonia water; add 1 cc. of magnesia mixture and 20 cc. of stronger ammonia water; allow to stand twelve hours, filter, using a prepared Gooch crucible; wash with 2.5 per cent ammonia water; dry at 100 C.; ignite at 700 C. for three hours; cool in a desiccator and weigh as magnesium pyroarsenate and calculate to arsenic; the arsenic content is not less than 12.50 per cent nor more than 13.50 per cent. Transfer about 0.25 Gm. of bismarsen accurately weighed to an Erlenmeyer flask. Add 5 cc. of diluted sulfuric acid followed by 1 Gm. of powdered potassium permanganate, and 10 cc. of sulfuric acid in small portions; add just sufficient hydrogen peroxide to dissolve the brown precipitate; add 50 cc. of water; boil for twenty minutes, cool to 70 C.; saturate with hydrogen sulfide for twelve hours; filter, using a prepared Gooch crucible; wash the precipitate with water, warm ammonium polysulfide, methyl alcohol, carbon bisulfide and acetone in the order named; dry at 100 C.; cool in a desiccator and weigh as bismuth sulfide ( $BuS_2$ ); calculate to bismuth, the percentage of bismuth found corresponds with the percentage of arsenic found multiplied by 1.86 (factor As to Bi in  $CuH_{12}O_{12}As_4Na_4S_4N_2Bi_4$ ) plus or minus 0.5 per cent.

#### ABBOTT LABORATORIES

**Ampoules Bismarsen:** 0.1 Gm. and 0.2 Gm.; accompanied respectively by 1 cc. and  $1\frac{1}{4}$  cc. ampuls of a sterile, aqueous solution of 0.25% Butyn Sulfate

U. S. patent 1,605,691 (Nov. 2, 1926, expires 1943). U. S. trademark 230,625.

**MAPHARSEN.**—The hemialcoholate of 3-amino-4-hydroxy phenylarsine oxide hydrochloride.— $HCl.(NH_2)C_6H_4(OH)AsO\frac{1}{2}C_2H_5OH$  It contains approximately 29 per cent of trivalent arsenic.



**Actions and Uses.**—Mapharsen is proposed for the treatment of syphilis. It is stated to exhibit a relatively constant parasitocidal value. It is claimed to have a rapidly beneficial effect, particularly on early syphilis, healing of lesions, and reversions in a large percentage of the use of mapharsen are less severe than those observed after the use of the arsphenamines.

**Dosage.**—Intravenously, 0.03 Gm. for women and 0.04 Gm. for men, initially. The dose may be increased at the second

injection to 0.04 Gm for women and 0.06 Gm for men. The maximum dose, which should not be given any patient at the first injection, may be regarded as 0.06 Gm to 0.07 Gm. Injection may be given every four or five days or in severe cases twice a week since it is excreted very rapidly from the kidney. For children the initial dose should not exceed 0.5 mg per kilogram of body weight; the total dose should average between 0.5 and 1 mg per kilogram of body weight.

It should be noted that the dosage of mapharsen is much lower than that of the arsphenamines.

The drug should be kept in the ice box.

### Tests and Standards—

Mapharsen occurs as a white amorphous odorless powder. It is soluble in water, alcohols, acids, alkalis and alkali carbonates. The aqueous solution is acid to methyl red but alkaline to congo red.

Add 0.5 Gm of sodium hydrosulfite to about 0.1 Gm of mapharsen dissolved in 10 cc of water; a yellow precipitate separates. Add sodium carbonate solution drop by drop to a 1 per cent aqueous solution of mapharsen; no precipitate is formed (*distinction from arsphenamine*). Add diluted hydrochloric acid to a 1 per cent aqueous solution of mapharsen; no precipitate is formed (*distinction from neoarsphenamine*).

Add 2 cc of colorless 20 per cent hydriodic acid to about 0.02 Gm of mapharsen; a color not deeper than a lemon yellow is produced (*3 amino 4 hydroxy phenyl arsonic acid*).

Transfer about 0.15 Gm of mapharsen accurately weighed to a wide mouth weighing bottle and dry to constant weight in a vacuum desiccator over phosphorus pentoxide; the sample loses not more than 2 per cent.

Dissolve about 0.1 Gm of mapharsen accurately weighed in 25 cc of distilled water; titrate with tenth normal iodine solution using a starch indicator; the trivalent arsenic is not less than 28.2 per cent nor more than 29.5 per cent.

Dissolve about 0.2 Gm of mapharsen accurately weighed in 5 cc.

with dilute ammonia water (1 volume of stronger ammonia water with 2 volumes of water; dry at 100° C; heat in a muffle furnace at 400° C for four hours; then gradually raise the temperature to 800° C; cool in a desiccator and weigh; the arsenic calculated on the dry basis is less than 30 per cent).

Dissolve about 0.1 Gm of mapharsen accurately weighed in about 25 cc of distilled water; titrate to the green color of bromthymol blue with tenth normal sodium hydroxide solution; the hydrogen chloride calculated on the dry basis is not less than 14.0 per cent nor more than 14.7 per cent.

### PARKE, DAVIS & COMPANY

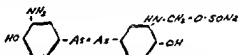
Ampoules Mapharsen 0.04 Gm and 0.06 Gm

Ampoules Mapharsen 0.4 Gm and 0.6 Gm *Caution*  
These ampouls are hospital packages and represent ten doses respectively.

Each of the ampuls of mapharsen contain the stated amount of the arsenical admixed with anhydrous sodium carbonate, 4.3 per cent and anhydrous sucrose, 81.4 per cent.

U. S. patents 2,092,028 and 2,092,036 (Sept. 7, 1937; expires 1954)  
U. S. trademark 299,173.

**NEOARSPHENAMINE.**—"Consists chiefly of sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-*N*-methanal sulfoxylate. It contains not less than 19 per cent of arsenic (As) and complies with the requirements of the National Institute of Health, United States Public Health Service." *U. S. P.*



For description and standards see the U. S. Pharmacopeia under Neoarsphenamina.

**Actions and Uses.**—Neoarsphenamine is a modified soluble compound of arsphenamine; its action and uses are those of arsphenamine.

**Dosage.**—Neoarsphenamine is probably less toxic than arsphenamine and, since it contains less arsenic, it is given in larger doses than arsphenamine. The average dose for a man is 0.45 to 0.60 Gm., with 0.45 Gm. as the minimum and possibly 0.75 Gm. as the maximum only for very large men. For women, 0.45 Gm. is the average if the patient is about the normal in weight; 0.3 Gm. would be the minimum and 0.6 Gm. the maximum, the latter dose being given only to large women. Children may be given 0.1 to 0.2 Gm. The limit dose is 15 mg. per kilogram of body weight. Here again a smaller dose is preferable.

Neoarsphenamine may be administered by intravenous or intramuscular injection, the former being considered decidedly preferable, the drug must not be administered subcutaneously. For intravenous gravity injection, 12.5 cc. of freshly distilled water should be used for each 0.1 Gm. of neoarsphenamine. For the intramuscular injection, 0.3 cc. of freshly distilled water should be used for each 0.15 Gm. of neoarsphenamine, this yielding an approximately isotonic solution.

Neoarsphenamine may be employed intravenously in concentrated solutions. For this purpose as much as 0.1 Gm. may be dissolved in 0.5 cc. of sterile freshly distilled water; the injection is made with a syringe instead of by gravity. It is well to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the blood stream. It should be injected very slowly.

The ampule containing the drug is immersed in alcohol to detect a possible crack, then carefully wiped off; the neck filed

across and broken off, and the contents sprinkled on the surface of cool, sterile distilled water and allowed to dissolve *without shaking* the solution. Any product incompletely soluble should be discarded. Solutions of neoarsphenamine must be injected *immediately* after their preparation. Neoarsphenamine must not be warmed and the temperature of the injected fluid should not be more than 20 to 22 C (68 to 71.6 F).

Neoarsphenamine may undergo deterioration in the ampule, and care should be exercised to use a drug of normal color and free solubility. The drug in fresh solution should be of canary yellow color. This drug should preferably be kept in a cool dark room or ice box and be not more than 6 months old.

*Caution*—Solutions of Neoarsphenamine must be freshly prepared when required for use. The solution should not be shaken during its preparation. U S P

#### ABBOTT LABORATORIES

Ampoules Neoarsphenamine: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 3.0 Gm., and 4.5 Gm.

Neoarsphenamine and Metaphen: Packages containing five ampoules of neoarsphenamine, 0.04 Gm. each, and one bottle of metaphen solution 1:1000 (20 cc.)

*Actions and Uses*—Neoarsphenamine and metaphen is proposed for the treatment of Vincent's gingivitis and stomatitis.

*Dosage*—Neoarsphenamine 0.04 Gm. is dissolved with 4 cc. of the 1:1000 aqueous solution of metaphen and the resultant solution is applied topically.

#### DIARSENOL COMPANY, INC.

Ampoules Neodiarsenol: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 1.8 Gm., 3.0 Gm., and 4.5 Gm.

#### MALLINCKRODT CHEMICAL WORKS

Ampoules Neoarsphenamine: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 3.0 Gm., and 4.5 Gm.

#### MERCK & CO., INC.

Ampoules Neoarsphenamine: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 3 Gm., and 4.5 Gm.

#### E. R. SQUIBB & SONS

Ampoules Neoarsphenamine: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 3.0 Gm., and 4.5 Gm.

#### WINTHROP CHEMICAL COMPANY, INC.

Neosalvarsan (Powder): bulk Neoarsphenamine

Ampoules Neosalvarsan: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 1.8 Gm., 3.0 Gm., and 4.5 Gm.



**SILVER ARSPHENAMINE.**—Arsphenamina Argentea.—Sodium Silver Arsphenamine.—The sodium salt of silver-diamino-dihydroxy-arseno-benzene (the exact molecular formula has not been established). Silver arsphenamine contains not less than 19 per cent of arsenic and from 12 to 14 per cent of silver.

*Actions and Uses.*—Silver arsphenamine has practically the same uses as those of arsphenamine. Its claimed advantage over other arsphenamine preparations is said to be due to the introduction of the silver (nonionizable form) as a component, thereby improving the chemotherapeutic index, presumably because of the fact that silver and its compounds have a decided antisyphilitic influence.

In the presence of organic diseases of the heart, such as aneurysm and aortitis, as well as in other parenchymatous disease conditions of the glandular structures (liver and kidney), silver arsphenamine should be used only with great caution and in small doses, the patient and all functions being observed most carefully.

Untoward symptoms noted after the use of arsphenamine and of neoarsphenamine have likewise been seen after the use of silver arsphenamine. Argyria may occur rarely as a sequel to the use of this preparation.

*Dosage*—From 0.1 Gm. to 0.3 Gm. for adults. The treatment should begin with an injection of 0.1 Gm., gradually increasing the dosage, at intervals of not less than four days, to 0.2 Gm. maximum in women and 0.3 Gm. in men. The larger doses are indicated only if the preparation is well tolerated by the patient. The doses of 0.2 to 0.25 Gm. may be given at regular intervals of 7 days and repeated until the desired therapeutic results have been achieved. Patients with disorders of the nervous system or those suffering from severe headaches should be given smaller initial doses, 0.05 and 0.075 Gm. When these amounts are well tolerated, larger doses may be employed, increasing very gradually.

In preparing the solution for injection, the ampule is first tested for cracks by immersion in alcohol for 15 minutes; after opening the ampule, the contents are sprinkled on the surface of 5 cc. of cool (20-22 C), sterile, distilled water, contained in a small sterile flask. The silver arsphenamine will go into solution rapidly; heating and shaking must be avoided. A quantity of cool sterile solution of sodium chloride, 0.4 per cent, is then added so that the final solution will approximate 20 cc. of liquid per decigram (0.1 Gm.) of the drug. *The solution must be administered promptly but slowly.*

#### *Tests and Standards.*—

Silver arsphenamine is prepared by treating the dihydrochloride of 3-diamino-4-dihydroxy-1-arsenobenzene (arsphenamine) with silver salts.

converting the resulting compound to the disodium salt and precipitating by means of alcohol, ether or acetone. The silver is not in an ionizable form.

Silver arspenamine is a brownish black powder, unstable in air; when properly dried it is free from lumps. It is readily soluble in water, yielding a dark brown solution (*distinction from arspenamine, sodium arspenamine and neoarsphenamine*), the solution has an alkaline reaction (*distinction from arspenamine*).

The addition of dilute sodium hydroxide solution to 3 cc of an aqueous solution of silver arspenamine (1 in 500) produces no precipitate (*distinction from arspenamine*). On the addition of 1 cc of sodium carbonate test solution to 1 cc. of silver arspenamine solution (1 in 20) no precipitate is formed (*distinction from arspenamine*). The addition of 1 cc of saturated solution of sodium bicarbonate to 1 cc of silver arspenamine solution produces a precipitate.

One cc. of an aqueous solution of silver arspenamine solution (1 in 20) when slightly acidulated with dilute hydrochloric acid yields a precipitate (*distinction from arspenamine*). This precipitate dissolves

from arspenamine), a portion of which dissolves on further addition of the acetic acid test solution. When 3 cc of silver arspenamine solution (1 in 20) is heated with a few crystals of potassium permanganate (*without addition of alkali, distinction from arspenamine*), the permanganate is reduced and ammonia is evolved which may be tested by placing a moistened piece of red litmus paper in the vapors; the litmus paper will turn blue. The precipitate thus formed may be treated with hot nitric acid test solution, the mixture is boiled for a few minutes and then cooled, diluted and filtered; the filtrate will yield a precipitate of silver chloride on the addition of hydrochloric acid (*distinction from arspenamine, neoarsphenamine and sodium arspenamine*). The addition of 1 cc. of silver arspenamine solution to 1 cc. of sodium chloride test solution to 1 cc. of a deepening of the brown coloration from sodium arspenamine more concentrated employed, an immediate precipitate is formed. The careful addition drop by drop, of bromine water to 3 cc of silver arspenamine solution (1 in 250) produces a reddish coloration which is discharged by an

arsphenamine, neoarsphenamine and sodium arspenamine). To 1 cc of silver arspenamine solution (1 in 20) add 1 cc of sodium chloride test solution; no precipitate forms (*absence of ionizable silver*). (A concentrated sodium chloride solution added to a strong solution of silver arspenamine causes a precipitate to form, due to a "salting out" action.)

Place about 0.2 Gm of silver arspenamine, accurately weighed in an Erlenmeyer flask and carry out the Lehman process (described in *Pub Health Rep* 33:1003 [June 21] 1918) through the point of digestion. While the solution is being digested, filter off the silver. Wash well and weigh. Percentage of silver is carried on in the usual manner according to the Lehman method.

thereby determining the arsenic content. The total silver content of the drug shall be from 12 to 14 per cent and the total arsenic content shall be not less than 19 per cent.

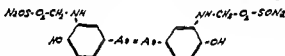
To determine the toxicity, select not less than five healthy albino rats weighing between 100 and 150 Gm. (pregnant animals shall not be used); prepare a 2 per cent silver arsphenamine solution and inject the solution into the saphenous vein of each rat at a rate of not more than 0.5 cc. per minute. The rats shall not be anesthetized for the injection. At least 60 per cent of the series of animals injected with the maximum tolerated dose should survive forty-eight hours from the time of injection: The maximum tolerated dose shall not be below 0.14 Gm. per kilogram of body weight.

### WINTHROP CHEMICAL COMPANY, INC.

Ampules Silver-Salvarsan: 0.1 Gm., 0.15 Gm., 0.2 Gm., 0.25 Gm., 0.3 Gm., and 0.6 Gm.

U. S. patent 1,127,603 (Feb. 9, 1915, expired). U. S. trademark 161,232.

**SULFARSPHENAMINE.**—"*Disodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene N,N'-dimethylacetate*." It contains not less than . . . to claims . . . chains in . . . (with an extra oxygen atom) and not two as in neoarsphenamine.



For description and standards see the U. S. Pharmacopeia under Sulfarsphenamina.

**Actions and Uses.**—The same as those of neoarsphenamine; it is probably somewhat more stable in solution in the presence of air, and it permits of intramuscular injection. In terms of percentages there seems to be a higher incidence of reactions following the use of sulfarsphenamine, far more, in fact, than after the use of the other arsenicals employed in the treatment of syphilis. These reactions consist in (a) dermatitis, (b) hemorrhagic eruptions, (c) meningo-vascular reactions, and (d) aplastic anemias. All patients under treatment with sulfarsphenamine should be followed closely by the physician for evidence of reaction. The drug has a place, and may be used by the intramuscular route in the treatment of early heredo-syphilis and in certain cases where the patient has such poor veins that intravenous therapy is out of the question. Moore considers it the drug of choice, by the intramuscular route in early congenital syphilis.

**Dosage.**—The maximum dosage by any route should probably not exceed 0.4 Gm., or at most 0.5 Gm. of the dry substance.

For intramuscular or subcutaneous use the drug is dissolved in sterile, freshly distilled water in the proportion of about 0.1 Gm. to 0.3 cc., the total volume being not more than 10 to

20 cc. There is probably less local reaction where a minimum of diluent is employed. For intravenous use the drug should be diluted in the proportion of 0.1 Gm. to not less than 10 and preferably, 40 cc., or more, the total volume amounting to 50 to 200 cc. or more. Dosage for infants is 0.01 Gm. to 0.015 Gm. per kilogram of body weight.

#### ABBOTT LABORATORIES

Ampules Sulfarsphenamine 0.1 Gm. 0.2 Gm. 0.3 Gm., 0.4 Gm. and 0.6 Gm.

#### MALLINCKRODT CHEMICAL WORKS

Ampules Sulfarsphenamine 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm., 0.9 Gm. and 3.0 Gm.

#### MERCK & Co., INC.

Ampules Sulfarsphenamine 0.1 Gm., 0.2 Gm. 0.3 Gm. 0.4 Gm. and 0.6 Gm.

#### E. R. SQUIBB & SONS

Ampules Sulfarsphenamine 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm. 0.6 Gm. 0.9 Gm. and 3.0 Gm.

#### WINTHROP CHEMICAL COMPANY, INC.

Ampules Sulfarsphenamine 0.1 Gm., 0.15 Gm. 0.3 Gm. 0.45 Gm. 0.6 Gm. 0.75 Gm. 0.9 Gm. and 3.0 Gm.

#### Compounds Containing Pentavalent Arsenic

**ACETARSONE**—Acetylaminohydroxyphenylarsonic Acid— $\text{HO-CH}_2\text{-CONH-C}_6\text{H}_4\text{-As(O)}_3$ —Stovarsol—The acetyl derivative of 3-amino-4-hydroxyphenyl-1-arsonic acid—Acetarsonone contains from 27.1 to 27.4 per cent of arsenic (As).



**Actions and Uses**—Acetarsonone has been reported to produce favorable effects in the treatment of amebiasis. Acetarsonone is useful as a means of medication of the vagina in the treatment of *Trichomonas vaginitis*. Its use in the treatment of sarcoid has been recommended by various dermatologists. Acetarsonone has been proposed for use both in prophylaxis and in treatment in certain cases of syphilis, but the evidence is thus far inconclusive. Its use in amebic infections undoubtedly is of value though still in the experimental stage. In using acetarsonone, the physician should remember that he is working with a rather

toxic arsenical preparation, which may give rise to gastro-intestinal symptoms and hepatitis as well as to the same cutaneous disturbances that are found with the arsphenamines, for example, urticaria, erythema of various types and even hemorrhagic eruptions. At the least sign of intolerance the physician should discontinue the use of the drug for the time being.

Acetarzone in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow; suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

**Dosage.**—Orally, 0.25 Gm. for adults, two or three doses a day for a period of seven days have been reported to give satisfactory results. For *Trichomonas vaginitis*, use locally in the vagina a powder containing 12½ per cent acetarzone in a mixture of equal parts of kaolin and sodium bicarbonate. Single dose 4 Gm.—1 teaspoonful of the mixture containing 0.5 Gm acetarzone. In case of pregnancy, if insufflation is employed, care must be taken to exert no positive pressure in the vagina.

#### *Tests and Standards.*—

Acetarzone is a white, odorless powder, having a slightly acid taste. It is slightly soluble in water and alcohol and readily soluble in solutions of alkalis or alkaline carbonates. It is stable at ordinary temperatures.

To a solution of 1 Gm. of acetarzone in 10 cc. of sodium hydroxide solution and 10 cc. of water, add 2 Gm. of sodium hydrosulfite and warm the mixture to about 50 C.; a light yellow precipitate is formed, which is soluble in an excess of sodium hydroxide. To a solution of 0.5 Gm. of acetarzone in 10 cc. of water, and a slight excess of ammonia water, add magnesia mixture; no precipitate forms (*absence of inorganic arsenates*), but on heating the mixture for some time, a precipitate is produced. Dissolve 1 Gm. of acetarzone in 10 cc. of sodium carbonate solution; no undissolved residue remains. To 1 Gm. of acetarzone add 10 cc. of hydrochloric acid (5 per cent), shake well and filter. To the filtrate add two drops of solution of potassium bichromate (3 per cent); no red or brown color is produced (*unacetylated*).

Shake 0.5 Gm. of acetarzone five minutes and then filter; the residue on the addition of a few drops of 5 per cent solution of sodium hydroxide should be completely dissolved. Dry a weighed quantity of acetarzone; the loss does not exceed 0.5 per cent.

Determine the arsenic of acetarzone by Lehmann's method; the arsenic content corresponds to from 27.1 to 27.4 per cent.

## ABBOTT LABORATORIES

Acetarsone (Powder): bulk

Tablets Acetarsone: 0.05 Gm., 0.1 Gm., and 0.25 Gm.

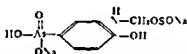
## MENCK &amp; CO., INC.

Stovarsol (Acetarsone) (Powder)

Tablet Stovarsol: 0.05 Gm., 0.1 Gm., and 0.25 Gm.

U. S. trademark 177,092

## PHENARSONE SULFOXYLATE — Aldarsone — Sodium



**Actions and Uses** — Phenarsone sulfoxylate, a pentavalent arsenical, may be used in the treatment of *Trichomonas vaginalis* vaginitis and central nervous system syphilis. While this agent probably possesses comparatively low toxic properties because of its arsenical nature the physician should be on guard against untoward reactions. Such reactions include dermal and hemopoietic changes, nitritoid reactions. Since phenarsone sulfoxylate is a pentavalent arsenic compound, every care should be exercised and visual and color field examinations made prior to drug therapy so that contraction of visual field or symptoms of blurring may be observed.

**Dosage** — For the treatment of central nervous system syphilis 1 Gm. of phenarsone sulfoxylate dissolved in 10 cc. of sterile distilled water administered intravenously once a week. The injections may be given continuously for periods of forty to fifty weeks. Concurrent bismuth therapy may be employed during a portion of the course of phenarsone sulfoxylate injection. Phenarsone sulfoxylate may be given as a supplement to fever therapy in the treatment of various forms of central nervous system syphilis.

For the treatment of *Trichomonas vaginalis* phenarsone sulfoxylate may be administered by insufflation of the powder (with kaolin) and in the form of a suppository. For insufflation the vaginal tract and external os of the cervix are thor-

oroughly cleansed and dried; then the contents of a 3 Gm. vial of phenarsonesulfoxylate with kaolin are introduced by an insufflator. A cautionary statement is issued on the use of positive pressure in the pregnant female when insufflation is employed. The escape of air from the vagina should be permitted during compressions in case the patient is pregnant. The patient is treated for three consecutive days. Then additional treatments are given at three day intervals. No douche should be taken during the treatment.

Phenarsonesulfoxylate suppositories may be used in conjunction with insufflation. They offer a way of providing phenarsonesulfoxylate between insufflation treatments. Suppository treatment is started no sooner than twenty-four hours after the last power treatment. One is inserted every second or third night until the patient reports for the next insufflation treatment. They may also be used alone by insertion of one suppository every third or fourth night for not more than three weeks. The patient should be warned against prolonged use of this treatment without the advice of a physician, since an arsenical is being employed. Suppositories alone should not be expected to produce permanent results: merely to lessen the discharge and diminish symptoms.

#### Tests and Standards—

... ..  
sulfoxylate dissolved in 5 cc. of water and warm at 50-60 C. for five minutes a yellow solution is produced, add normal hydrochloric acid dropwise to the solution a lemon yellow gelatinous precipitate forms, soluble in excess hydrochloric acid. Add 1 cc. of iodine solution and 2 cc. of chloroform to 10 cc. of a 1 per cent solution of phenarsonesulfoxylate; shake the test tube and contents and then allow the liquids to separate: no color appears in either of the liquid layers. Repeat the test, first adding 0.25 Gm. of sodium bicarbonate: no color appears in the chloroform layer, but the aqueous layer is colored light brown. Add 2 cc. of diluted nitric acid and 1 cc. of silver nitrate solution to 5 cc. of a 1 per cent solution of phenarsonesulfoxylate: a black precipitate forms: heat to boiling and cool: the mixture rapidly changes to a ... ..

valent arsenicals).

Dissolve 0.1 Gm. of phenarsonesulfoxylate in 5 cc. of water, add 0.5 cc. of a 10 per cent sodium hydroxide solution containing no red ... ..  
hydroxyphenylarsonic acids

Dissolve 0.5 Gm. of phenarsonesulfoxylate in 10 cc. of water, add 1 cc. of diluted ammonia water and 1 cc. of magnesium mixture: no precipitate forms (absence of inorganic arsenate). Heat the solution to boiling: a white precipitate forms slowly.

Dry an accurately weighed 1 Gm. portion of phenarsonesulfoxylate contained in a weighing bottle not less than 20 mm. diameter over fresh phosphorus pentoxide for twenty-four hours in a vacuum of at least 5 mm. of mercury: the loss in weight is not more than 2.5 per cent.

Transfer about 0.5 Gm of phenarsone sulfoxylate accurately weighed

residue responds to tests for sodium

Transfer about 0.5 Gm of phenarsone sulfoxylate, accurately weighed, to a 250 cc wide mouthed Erlenmeyer flask, add 10 cc of water to dissolve the sample taken and then add 15 cc of 30 per cent hydrogen peroxide. Mix and add 10 cc of sulfuric acid slowly down the side of the flask shaking the mixture after each addition. Place a short

acid solution to dissolve any crystals of hydrazine sulfate and then maintain heat sufficient to produce fumes of sulfur trioxide, which show a partial condensation point about 2 inches from the top of the flask for twenty minutes. Cool, dilute (*carefully*) with 20 cc of distilled water, add from 3 to 5 drops of a methyl orange solution (3 cc of methyl orange test solution diluted to 100 cc with water) and titrate while hot with tenth normal potassium bromate solution until the solution becomes colorless. Near the end point the potassium bromate solution should be added dropwise. Each 1 cc. of tenth normal potassium bromate is equivalent to 0.003746 Gm of arsenic. The amount of arsenic found is not less than 17.0 per cent nor more than 18.5 per cent.

#### ANNOTT LABORATORIES

**Aldarsone (Powder):** Phenarsone sulfoxylate 0.5 Gm and 1 Gm ampuls

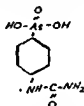
**Aldarsone Vaginal Suppositories:** Each suppository contains phenarsone sulfoxylate 0.13 Gm in a glycerogelatin base



**Aldarson** with Kaolin: 30 Gm. Each 3.0 Gm contains phenarsonic sulfoxylate 0.5 Gm and kaolin 2.5 Gm. packaged in glass tubes suitable for use with insufflator.

U. S. Pat. No 2,074,757. U. S. Trademark: 338,986

**CARBARSONE.**—"When dried at 80° C. for 6 hours, contains from 281 to 288 per cent arsenic (As)." U. S. P.



For description and standards see the U. S. Pharmacopeia under Carbarsonum.

**Actions and Uses.**—Carbarsonic acid is proposed for the treatment of intestinal amebiasis. It is administered usually by mouth; in acute amebic dysentery or in resistant cases with motile amebas in the stools, retention enemas may be employed. While carbarsonic acid is said to be less toxic than acetarsone and serious untoward effects appear to be uncommon, cutaneous disturbances and other reactions common to arsenic compounds have been reported. The administration of carbarsonic acid may lead to injury of the optic nerve. While visual disturbances appear to be quite rare, the possibility of their occurrence should nevertheless be kept in mind during the therapeutic use of the drug. A moderate increase in intestinal activity may be observed. Carbarsonic acid, in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow; suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

**Dosage**—Orally, for adults, the usual dose is 0.25 Gm twice a day for ten days. If necessary this may be repeated following a ten day rest period. For children, the dosage may be reduced according to weight. As retention enemas, for adults, 2 Gm of the drug dissolved in 200 cc of warm 2 per cent sodium bicarbonate solution may be administered following a cleansing alkaline enema every other night for a maximum of five doses if necessary. Because of the large dosage employed (a total of 10 Gm over a period of nine days) oral administration should be interrupted during this interval.

#### ELI LILLY AND COMPANY

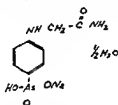
Carbarsone (Powder) 2 Gm vial

Pulvules Carbarsone 0.25 Gm

Suppositories Carbarsone 0.12 Gm

Tablets Carbarsone 0.05 Gm and 0.25 Gm

**TRYPARSAMIDE**—When dried to constant weight at 110° C, contains not less than 25.1 per cent and not more than 25.5 per cent of arsenic (As) "U S P"



For description and standards see the U S Pharmacopeia under Tryparsamudum

**Actions and Uses**—Tryparsamide was first used as a trypanocidal agent especially in the treatment of trypanosomiasis due to *T. gambiense* but is now used as well in resistant cases of syphilis of the central nervous system.

Tryparsamide has some spirocheticidal activity and has an unusual power of therapeutic penetration, especially in case of the central nervous system. The best results seem to have been obtained in patients with early dementia paralytica, it is estimated that perhaps from 40 to 50 per cent of such cases have shown varying degrees of symptomatic improvement. Tabetic affections have responded less satisfactorily, and patients with dementia paralytica with advanced mental and physical deterioration have shown little or no improvement. On the other hand, the drug may hasten the progress of the disease in such cases. Its use is considered inadvisable in forms of syphilis other than that of the central nervous system. It is being used quite extensively as the follow up treatment after malaria therapy in syphilis of the central nervous system.

The toxic effects of tryparsamide resemble those of other pentavalent arsenic compounds; the worst of these is the tendency to produce amblyopia, but cases of nitritoid reactions, of jaundice, of agranulocytosis, and of toxic hepatitis have also been reported. Before using the drug, careful consideration should be given to the frequent production of visual injury, which may be serious and permanent. This caution is especially important if the neurosyphilis has involved the optic nerve, causing contraction of the visual and color fields. The drug is, of course, contraindicated in conditions characterized by such contraction. The eyeground fields, including color fields, should always be mapped out before its use is undertaken and should be checked several times thereafter. Sometimes after one or two injections the patient will complain of blurred vision for a few days. In such cases treatment with tryparsamide should be discontinued, the visual fields determined at least weekly for three to four weeks, and then, if there is no evidence of damage to the optic nerve, the injection resumed, using great caution, minimal dosage at first, and checking the visual field preceding each injection. The drug is said to "have no virtues in ophthalmic syphilis."

**Dosage**—From 1.0 to 3.0 Gm for adults, depending on the purpose for which the drug is used. In general, the dose should not exceed 0.04 to 0.05 Gm. per kilogram of body weight, and such doses should not be repeated at intervals of less than one week. Tryparsamide is employed by the intravenous route. The drug is dissolved in sterile water or physiologic solution of sodium chloride. Tryparsamide should never be administered by mouth.

MERCK & CO., INC.

Tryparsamide (Powder): 50 Gm bottle.

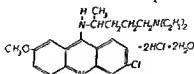
Tryparsamide Ampuls: 1 Gm, 2 Gm and 3 Gm

U. S. patents 1,280,119, 1,280,120, 1,280,121, 1,280,122, 1,280,123, 1,280,124 and 1,280,126 (Sept. 24, 1918; expired) by license of the Rockefeller Institute for Medical Research. U. S. trademark 186,022

### Quinacrine Compounds

**QUINACRINE** . . . . .  
Hydrochloride  
not less than 7  
quinacrine base  
98 per cent of

Mepacrine  
—"Contains  
per cent of  
less than



For description and standards see the U. S. Pharmacopeia under *Quinacrine Hydrochloridum* and *Tabellae Quinacrine Hydrochloridi*.

*Actions and Uses*—Quinacrine hydrochloride destroys the asexual forms (trophozoites) of the causative organism in all types of malaria and thus checks the progress of the disease. Given during the first paroxysms of a benign tertian (*P. vivax*) attack it will often prevent completely the appearance of the third paroxysm while considerably lessening the severity of the second. At present the consensus is that in ordinary cases of benign type, and also in the more rare quartan (*P. malariae*) type, it gives as good results as quinine. Some observers are of the opinion that relapses are less frequent than with quinine and that the period of treatment is shorter. Quinacrine hydrochloride is considered by some inferior to, by some equal to, and by others more effective than quinine in the treatment of malignant subtertian (*P. falciparum*) malaria. It is of value in the treatment of blackwater fever when the treatment of quinine is contra-indicated. Like quinine the drug effects partial destruction of the sexual forms (gametocytes) of the malarial organisms and thus lessens in some degree the extent to which the patient may act as a reservoir from which mosquitoes may be infected; this action is, however, least pronounced in the malignant subtertian form. If taken faithfully in prophylactic dosage quinacrine hydrochloride will reduce the incidence of frank clinical malaria, being in this regard perhaps somewhat more effective than quinine.

Quinacrine hydrochloride is reported to be effective in combating *Giardia lamblia* infestation but the evidence that this organism is pathogenic for man or is the cause of diarrhea and other symptoms associated with its presence in the gastrointestinal tract is inconclusive.

Quinacrine hydrochloride causes the urine to become very yellow on the third to fifth day, and, being of an acridine dye nature, it may cause discoloration of the skin, the latter persisting usually no longer than two weeks. Headache and relatively mild gastrointestinal symptoms occur but not very frequently. The drug does not cause visual or aural disturbances and may therefore be preferred to quinine by patients who have experienced both drugs. The circulatory system does not seem to be disturbed by quinacrine hydrochloride in therapeutic dosage. The drug is not considered to be toxic to the liver or kidneys. Some patients claim to be stimulated by quinacrine hydrochloride. A relatively small number of psychotic attacks have been attributed to the drug—some quite severe—but no permanent derangements have been recorded. Apparently the drug may be used with safety in any stage of pregnancy though many observers withhold it in toxemia.

Quinacrine hydrochloride is absorbed readily from the intestine and is excreted slowly in the urine and feces. It is usually

given by mouth but may also be given intravenously or intramuscularly, the latter route being preferred if injection must be resorted to at all.

**Dosage**—Oral. Adults: 0.1 Gm three times daily for five days. Children of 1 to 4 years: 0.05 Gm. twice daily for five days or once daily for eight days, crushed and suspended in honey or syrup. Children of 4 to 8 years: 0.1 Gm. twice daily for five days or once daily for eight days. Children over 8 years: Dosage like that of adults.

**Prophylactic Dose**: Adults: 0.2 Gm. twice weekly, or 0.05 Gm. daily. Children: 0.05 Gm. every other day.

The technic of the intramuscular or intravenous administration must be learned before the method is used. Details will be found in the circulars of manufacturers and in various publications.

#### WINTHROP CHEMICAL COMPANY, INC.

**Ampules Atabrine di-Hydrochloride Powder**: 0.2 Gm packaged with 10 cc. ampuls of sterile distilled water

**Tablets Atabrine di-Hydrochloride (Sugar Coated)**: 0.1 Gm.

**Tablets Atabrine di-Hydrochloride**: 0.05 Gm. and 0.1 Gm

U. S. patent 2,113,357 (April 5, 1938; expires 1955). U. S. trademark 302,473.

#### Bismuth Compounds

Until 1921 bismuth had been used particularly in the treatment of intestinal infections, as a paste for tuberculous fistulae and in radiology. Sauton and Robert then showed the value of sodium potassium bismuth tartrate in trypanosomiasis and spirillosis of fowls. Sazerae and Levaditi then took up the treatment of syphilis with the same drug. From this time on the value of bismuth preparations for treating syphilis has been more and more realized and its general use has been increased enormously throughout the world. Bismuth seems to have both a spirocheticidal and a spirochetostatic effect.

For use in the treatment of syphilis, the administration of the greater number of this type of bismuth preparations by the mouth has not proved satisfactory nor has the value of bismuth injections been shown. Thus far the best results with bismuth therapy of syphilis have been achieved by intramuscular injections. Probably those compounds of bismuth will have the best spirocheticidal value that are able to keep the therapeutic level of bismuth in the blood stream at such a continuous height that it will be reflected in the urine with a level of 0.002 Gm. or more of metallic bismuth per day. Intravenous injections are strictly contraindicated for the reason that the therapeutic dose approaches too closely to the toxic dose. The compounds employed for intramuscular injection con-

sist of water soluble salts dissolved in aqueous solution or other suitable solvents, or suspended in oils, of insoluble bismuth salts suspended in water or oils, of so called oil soluble preparations of water soluble and oil suspended combinations and finally of bismuth and arsenic compounds. The so called oil soluble preparations are claimed to be more exact in their dosage than insoluble suspensions of bismuth salts. They are said not to be absorbed and excreted so rapidly as the soluble bismuth preparations. Yet the claim is made that they are absorbed more rapidly than the insoluble bismuth salts in suspension. Thus the claim is made that they combine some of the advantages of both the soluble and of the insoluble preparations. This question has not been entirely and satisfactorily answered as yet. Thus far it seems to be the generally accepted opinion that bismuth salts used in the treatment of syphilis should be administered by the intramuscular route. In giving the intramuscular injections of the bismuth salts the needle should be inserted in the inner angle of the upper and the outer third of the buttocks, deep down into the muscular tissue. With the syringe tip inserted into the needle the physician should aspirate back with the plunger of the syringe in order to be sure that the needle is not in a vein or in an artery. This will go far toward obviating many of the distressing venous emboli and arterial emboli that have been reported. Those who have worked with bismuth salts in treating syphilis believe that their efficiency stands between that of mercury and that of arsphenamine. The present evidence appears to show that there is warrant for the administration of bismuth compounds in the treatment of syphilis in connection with arsphenamine or as a substitute for mercury therapy. Some few syphilologists use bismuth therapy alone in treatment of syphilis. These men are much in the minority however. Bismuth compounds are most valuable in the treatment of syphilis in patients who are intolerant to other drugs or who show resistance to other drugs used in syphilis e. g. the arsenic fast individual or so called arsenic intolerant individual. However, there is far more chance of curing a patient with syphilis where the physician is able to use both arsenical therapy and bismuth therapy either in alternating courses or, in certain instances in a combined fashion. Treatment with bismuth preparations is not usually injurious if the necessary precautions are taken (careful observation of the skin for untoward reaction of the mouth for signs of beginning bismuth stomatitis and of the urine for evidence of irritation of the kidneys).

Until the controversy concerning the penetration of appreciable amounts of special bismuth salts into the tissues of the central nervous system and of their presence in the spinal fluid is settled by more convincing evidence it appears unwise to accept therapeutic implications based on such claims.

In common with another heavy metal mercury bismuth preparations when administered by injection have a definite

diuretic action. Excretion studies of various bismuth compounds used in the treatment of syphilis give some indications as to the best type of bismuth salts for desired results. The usefulness of a bismuth preparation involves the concentration of active bismuth attained in the tissues, especially in the blood, and the height, course, rise, duration and decline of this concentration. As a rule, watery solutions, if repeated

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is a slower absorption and concentration in the blood stream, but one which persists longer, thus requiring injections but once a week. Certain of the oil solutions have like characteristics, with an added more rapid absorption than the oil suspensions. Bismuth subsalicylate is more slowly absorbed and there is a somewhat longer delay before the bismuth effect is achieved. Moreover, in small amounts it continues to be excreted over long periods of time, even months after injections are stopped. Whether this long excretion indicates a therapeutic level of the drug in the body is doubtful.

**BISMO-CYMOL.**—A basic bismuth salt of camphocarboxylic acid (camphor-3-carboxylic acid) having the probable formula  $(C_{10}H_{18}OCCO)_2BiOBi(C_{10}H_{18}OCCO)OH$ . It contains between 37 and 40 per cent of bismuth.

**Actions and Uses.**—Bismo-cymol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds). Bismo-cymol belongs to the class of so called liposoluble bismuth compounds which, because of their solubility, are absorbed more rapidly than insoluble bismuth salts, approaching that of soluble bismuth salts. T

toxicity for this  
the gums closely

**Dosage.**—Bismo-cymol is injected intramuscularly in doses representing 0.1 Gm. of metallic bismuth once a week or in doses representing 0.05 Gm. of metallic bismuth twice a week for from eight to ten weeks.

#### Tests and Standards—

Bismo-cymol occurs as a white powder having the odor of camphor. It is insoluble in water but soluble in ether, benzene and vegetable oils.

Heat 1 Gm. of bismo-cymol in 30 cc. of water containing 3 cc. of hydrochloric acid, add ammonia water until resulting solution is alkaline to litmus, filter and wash the precipitate with 7 cc. of water, to the filtrate add hydrochloric acid until just acid to litmus, evaporate on the steam bath until the volume is reduced one half, cool, filter and dry the crystals; the crystals melt at 127° C. Dissolve 0.1 Gm. of the crystals in 5 cc. of alcohol, add a drop of diluted ferric chloride solution (ferric chloride solution diluted 1 to 5), a green color results. Dissolve the precipitate obtained from the treatment with

ammonia water) in diluted hydrochloric acid and pass in hydrogen sulfide, a black precipitate forms. Suspend 0.2 Gm of bismo-cymol in 10 cc of boiling water and add 2 Gm of sodium hydrosulfite a black precipitate forms.

Add 5 cc of sodium hydroxide solution and about 0.2 Gm of aluminum wire to about 0.2 Gm of bismo-cymol, heat gently the vapors do not turn red litmus blue (nitrate). Suspend 0.25 Gm in 30 cc. of water, add 4 cc diluted nitric acid boil, cool, filter and add 1 cc of silver nitrate solution no more turbidity is produced than in the U. S. P. test for chlorides using 0.1 cc. of five per cent hydrochloric acid (chloride). Suspend 0.1 Gm in 30 cc of water, add 4 cc of diluted hydrochloric acid, boil, cool, filter, add 1 cc of barium chloride solution and dilute to 50 cc no turbidity is produced in ten minutes (sulfate). Add 2 cc of nitric acid to 2 Gm of bismo-cymol in a porcelain crucible, evaporate to dryness on the steam bath, ignite, add 5 cc of hydrochloric acid and 10 cc of a saturated solution of stannous chloride in hydrochloric acid the mixture does not darken in thirty minutes (arsenic). Ignite 3 Gm of bismo-cymol in a quartz crucible, cool, add drop by drop just enough nitric acid to dissolve the residue when warmed pour the acid solution into 100 cc of distilled water, evaporate to 30 cc., filter if necessary and divide into 5 cc portions. To one portion add an equal quantity of diluted sulfuric acid the liquid does not become cloudy (lead). To another portion add an excess of ammonia water the liquid does not exhibit a bluish tint (copper). To another portion add 0.5 cc of diluted hydrochloric acid a precipitate insoluble in an excess of hydrochloric acid and soluble in ammonia water is not formed (silver).

Transfer about 0.2 Gm of bismo-cymol, accurately weighed, to an Erlenmeyer flask, add 1 Gm of powdered potassium permanganate and then 5 cc of diluted sulfuric acid, allow to stand ten minutes, add 10 cc of sulfuric acid in small portions allow to stand fifteen minutes, decolorize with hydrogen peroxide, add 25 cc of water, boil for fifteen minutes, pass in hydrogen sulfide until the bismuth is completely precipitated filter through a prepared gooch crucible, wash with water, alcohol, chloroform and ether in this order, dry in an oven for thirty minutes at 100 C cool in a desiccator and weigh repeat the washing with chloroform and ether and the drying at 100 C until constant weight is attained. The weight of bismuth sulfide corresponds to not less than 37 nor more than 40 per cent bismuth.

#### ABBOTT LABORATORIES

**Ampules Solution Bismo-Cymol.** 1 cc and 2 cc. Each cc contains bismo cymol equivalent to 50 mg of metallic bismuth, dissolved in olive oil.

**Solution Bismo-Cymol:** 60 cc and 500 cc bottles. Each cc contains bismo cymol equivalent to 50 mg of metallic bismuth dissolved in olive oil.

U S patent 1,921,618 (Aug 8, 1933, expires 1950) U S trade mark 277,960

**BISMOSOL**—A sterilized solution of potassium sodium bismuthotartrate (containing 35 per cent bismuth [Bi]) 10 Gm, piperazine, 0.3 Gm, in an aqueous solution of glucose, to make 100 cc. Preserved with 0.1 mg n-butyl parahydroxybenzoate.

**Actions and Uses**—Bismosol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).



**Dosage.**—Bismosol is administered intramuscularly in doses of 1 cc. every two days until twenty doses have been given. After an intermission of one month, a second course may be given.

**Tests and Standards.**—

Bismosol is a pale yellow, syrupy liquid. On adding diluted hydrochloric acid, drop by drop, to bismosol, a gelatinous precipitate is formed which redissolves on further addition of the acid; the resulting solution yields a brownish black precipitate when saturated with hydrogen sulfide. On evaporation and ignition, bismosol yields an alkaline residue which effervesces with acids.

To 1 cc. of bismosol add three drops of acetic acid, a few drops of solution of hydrogen peroxide, one drop of ferrous sulfate solution and then an excess of sodium hydroxide solution; a purple violet color is produced. To 1 cc. bismosol add diluted hydrochloric acid drop by drop, until the precipitate which is formed has redissolved, and then add a few cubic centimeters of potassium bismuth iodide solution; a brilliant red precipitate is produced.

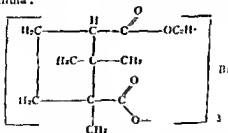
To 5 cc. of bismosol add about 100 cc. water and sufficient hydrochloric acid to redissolve the precipitate first formed, heat the solution to from 70 to 80 C., and saturate with hydrogen sulfide to precipitate completely the bismuth as bismuth sulfide. Collect the bismuth sulfide on a tared Gooch crucible, wash successively with water, alcohol, carbon disulfide and alcohol; dry to constant weight at 110 C. The weight of bismuth sulfide is equivalent to 3.5 Gm. of bismuth (Bi) in 100 cc. of bismosol.

**MERCK & Co., Inc.**

**Ampule Solution Bismosol:** 1 cc. Preserved with 0.1 mg. *n*-butyl parahydroxybenzoate.

U. S. trademark 196,017

**BISMUTH ETHYLCAMPHORATE.**—The bismuth III salt of *d*-camphoric acid mono-ethyl ester. It possesses the following formula:



$[C_{12}H_{18}O_4]_3Bi$ .—M. W. 890.8 It may be prepared by the interaction of sodium ethylcamphorate and bismuth nitrate in dilute aqueous glycerin solution. The product may then be extracted with chloroform and recovered by the removal of that solvent.

**Actions and Uses.**—Bismuth Ethylcamphorate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis. It is a liposoluble compound not so readily absorbed as the water soluble preparation and yet more

rapidly absorbed than the suspensions of insoluble bismuth salts in oil. Injection intramuscularly of this preparation produces relatively little local reaction.

**Dosage**—For the average adult, 2 cc. (80 mg. of metallic bismuth), administered once a week for a series of ten to fifteen injections.

### Tests and Standards—

Bismuth ethylcamphorate occurs as a white amorphous solid, possessing a faint aromatic odor. It is insoluble in water but soluble in chloroform, ether, ethylene dichloride and vegetable oils. Its solubility in the latter is increased by the addition of camphor. Bismuth ethylcamphorate softens at about 55 C. and melts indefinitely between 61 and 67 C.

Dissolve about 0.25 Gm. of bismuth ethylcamphorate in 25 cc. of ether in a separator, add diluted sulfuric acid sufficient to redissolve the white precipitate which forms at first, shake the mixture and then separate and wash the ether layer once with water. The aqueous acid layer responds to tests for bismuth. Extract the ether layer twice with 25 cc. portions of sodium hydroxide solution, evaporate the combined alkaline extracts in a beaker to a volume of about 15 cc., cover the beaker with a watch glass and continue to heat for about two hours, filter cool and acidify the solution with diluted sulfuric acid and allow the precipitate to crystallize. Separate and recrystallize the product from a small amount of hot water. The melting point of the dried d-camphoric acid obtained is from 146 to 183 C.

Fuse 0.25 Gm. of bismuth ethylcamphorate accurately weighed, in a tared, wide dish, heat at 75-80 C. under pressure of 10 to 15 mm. of mercury to constant weight; the loss in weight is not more than 2.5 per cent.

Transfer about 0.5 Gm. of bismuth ethylcamphorate accurately weighed, to a 250 cc. Erlenmeyer flask, add 15 cc. of sulfuric acid and 15 cc. of nitric acid and boil gently until the mixture is colorless, add 10 cc. more nitric acid if necessary. Continue to boil until the excess nitric acid is removed, cool and transfer the acid solution to a beaker, rinsing the flask with several 15 cc. portions of water. Dilute to about 100 cc., add two drops of methyl red solution and add ammonia water dropwise until the solution turns yellow. Add 2 cc. of nitric acid and dilute to about 150 cc. Heat to boiling, add five drops of 10 per cent ammonium phosphate solution and stir vigorously. Then add 40 cc. of the phosphate solution and digest the precipitate on a steam bath for thirty minutes, filter through a tared Gooch crucible and wash the precipitate with 5 per cent ammonium nitrate solution acidified with nitric acid. Dry at 100 C. for thirty minutes and finally ignite to constant weight. The weight of the bismuth phosphate found corresponds to a bismuth content of not less than 21.5 per cent nor more than 23.5 per cent, calculated to the dried substance.

### THE UPJOHN COMPANY

**Bismuth Ethylcamphorate Solution (in oil)** Vials 30 cc. Each cubic centimeter of solution contains a suspension of bismuth ethylcamphorate equivalent to 0.04 Gm. of elemental bismuth, camphor 0.10 Gm. and benzyl alcohol 0.025 cc., dissolved in peanut oil.

**Ampuls Bismuth Ethylcamphorate Solution (in oil)** 1 cc. Each cubic centimeter of solution contains a suspension of bismuth ethylcamphorate equivalent to 0.04 Gm. of elemental bismuth, camphor 0.10 Gm. and benzyl alcohol 0.025 cc., dissolved in peanut oil.

**BISMUTH SODIUM TARTRATE.**—Bismuth and Sodium Tartrate.—A basic sodium bismuth tartrate containing from 72.7 to 73.9 per cent of bismuth.

*Actions and Uses*—Bismuth sodium tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds). The drug has a definite diuretic action.

*Dosage.*—0.03 Gm by intramuscular injection, preferably into the gluteal muscle. The initial dose is 0.015 Gm, increased to 0.03 Gm with the second dose and continued in three doses weekly for from six to ten weeks.

*Tests and Standards*—

Bismuth sodium tartrate is a finely divided, white powder, odorless and tasteless; permanent in air. The product is soluble in about three parts of water, except for a slight residue (0.1 per cent); the residue is soluble in sodium hydroxide solution. The aqueous solution is alkaline to litmus paper. When acid is added gradually to an aqueous solution of bismuth sodium tartrate a precipitate is produced, which dissolves on the gradual addition of an alkali.

Dissolve 0.5 Gm. of bismuth sodium tartrate in 25 cc of water; heat to 50 C; add 1.5 Gm. of sodium hydrosulfite dissolved in 5 cc. of 10 per cent ammonia water; a precipitate of metallic bismuth

is formed. The precipitate is washed with water, dried, and weighed. The weight of bismuth is not less than 72.7 per cent.

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72.7 per

G. D. SEARLE & Co.

**Ampoules Solution Bismuth Sodium Tartrate, 1.5 per Cent:** 2 cc. Bismuth sodium tartrate, 0.03 Gm, benzyl alcohol 0.040 Gm., sucrose 0.50 Gm. in distilled water to make 2 cc.

**Ampoules Solution Bismuth Sodium Tartrate, 3 per Cent:** 2 cc. Bismuth sodium tartrate, 0.06 Gm.; benzyl alcohol 0.040 Gm., and sucrose, 0.50 Gm, in distilled water to make 2 cc.

**Solution Bismuth Sodium Tartrate, 1.5 per Cent:** 60 cc vial. An aqueous solution containing bismuth sodium tartrate 0.03 Gm, benzyl alcohol 0.04 Gm, and sucrose 0.50 Gm, in 2 cc.

**Solution Bismuth Sodium Tartrate, 3 per Cent:** 60 cc vial. An aqueous solution containing bismuth sodium tartrate 0.03 Gm, benzyl alcohol 0.02 Gm, and sucrose 0.25 Gm, in one cubic centimeter.

U. S. patents 1,663,201 (March 20, 1928; expires 1945) and 1,801,433 (April 21, 1931; expires 1948).

**BISMUTH AND POTASSIUM TARTRATE**—Potassium Bismuth Tartrate—Potassium Bismuthyl Tartrate—"A basic bismuth potassium bismuthotartrate, containing the equivalent of not less than 60 per cent and not more than 64 per cent of bismuth (Bi)." U. S. P.

For description and standards see the U. S. Pharmacopeia under Bismuthi et Potassii Tartras and Injectio Bismuthi et Potassii Tartratis.

**Dosage**—(a) *Oil Suspension*—From 0.1 to 0.2 Gm by intramuscular injection preferably into the gluteal muscle. The injections may be repeated at intervals of seven days until a total of from 2.4 to 3.0 Gm has been given. (b) *Aqueous Isotonic Solution*—50 mg by intramuscular injection preferably into the gluteal muscles three times a week until a total of 12 to 18 injections has been given.

#### ABBOTT LABORATORIES

**Ampoules Potassium Bismuth Tartrate (Aqueous)** 2 cc. Each ampul contains potassium bismuth tartrate, 0.05 Gm (equivalent to 32 mg elemental bismuth) in an aqueous solution containing cresol 0.2 per cent and sucrose 6 per cent.

**Ampoules Suspension Potassium Bismuth Tartrate with Butyn** 2 cc. Each ampul contains potassium bismuth tartrate 0.2 Gm and butyn 0.4 per cent with metaphen 1:20,000 suspended in peanut oil.

**Potassium Bismuth Tartrate (Aqueous) 2.5 per Cent** 60 cc bottle. Potassium bismuth tartrate 2.5 per cent in an aqueous solution containing cresol 0.2 per cent and sucrose 6 per cent.

**Potassium Bismuth Tartrate in Oil 10 per Cent with Butyn** 60 cc bottle. Each cc contains potassium bismuth tartrate 0.1 Gm (equivalent to 64 mg elemental bismuth) butyn 0.4 per cent and metaphen 1:20,000 suspended in peanut oil.

**Minck & Co., Inc.**  
**Bismuth and Potassium Tartrate (Powder)** bulk

**BISMUTH SUBSALICYLATE.**—Basic Bismuth Salicylate.—“A basic salt, which, when dried over sulfuric acid for 18 hours yield upon ignition not less than 62 per cent and not more than 66 per cent of  $\text{Bi}_2\text{O}_3$ .” *U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under Bismuthi Subsali-cylas and Injectio Bismuthi Subsali-cylatis.

#### ABBOTT LABORATORIES

**Bismuth Subsali-cylate with Butyn in Oil:** 30 cc., 60 cc., and 500 cc. bottles. A 10 per cent suspension of bismuth subsali-cylate in peanut oil to which has been added 0.4 per cent of butyn base and metaphen 1:20,000. Each cubic centimeter represents 0.057 Gm. of elemental bismuth.

**Ampoule Bismuth Subsali-cylate with Butyn in Oil:** 1 cc. A 10 per cent suspension of bismuth subsali-cylate in peanut oil to which has been added 0.4 per cent of butyn base and metaphen 1:20,000. Each cubic centimeter represents 0.057 Gm. of elemental bismuth.

#### CHEPLIN BIOLOGICAL LABORATORIES

**Ampuls Bismuth Subsali-cylate in Oil with Chlorobutanol 3%:** 0.13 Gm. in 1 cc. A suspension of bismuth subsali-cylate in olive oil containing in each cubic centimeter 0.13 Gm. of bismuth subsali-cylate and chlorobutanol 3 per cent.

**Bismuth Subsali-cylate in Oil with Chlorobutanol 3%:** 30 cc., 60 cc., 100 cc. and 480 cc. bottles. A suspension of bismuth subsali-cylate in olive oil containing in each cubic centimeter 0.13 Gm. of bismuth subsali-cylate and chlorobutanol 3 per cent.

#### DIARSENOL COMPANY, INC.

**Bismuth Subsali-cylate in Oil with Chlorobutanol 3%:** 30 cc., 60 cc., and 100 cc. bottles. A suspension of bismuth subsali-cylate in peanut oil, each cubic centimeter containing 0.13 Gm. of bismuth subsali-cylate (equivalent to 75 mg. of Bi metal) and 0.03 Gm. (3 per cent) of chlorobutanol.

#### THE DRUG PRODUCTS CO., INC.

**Hyposols Bismuth Subsali-cylate with Chlorobutanol 3% in Oil:** 60 cc. vial. This multiple dose vial contains in each cubic centimeter bismuth subsali-cylate 130 mg., chlorobutanol anhydrous 30 mg. and olive oil q. s.

#### ENDO PRODUCTS, INC.

**Ampuls Bismuth Subsali-cylate in Oil with Chlorobutanol 3%:** 2 cc. A suspension of bismuth subsali-cylate in peanut oil containing in each cubic centimeter bismuth sub-

salicylate U S P equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent of chlorobutanol

**Bismuth Subsalicylate in Oil with Chlorobutanol 3%**  
20 cc, 60 cc and 100 cc bottles A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate U S P equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent chlorobutanol

**THE GILLI AND LABORATORIES INC**

**Bismuth Subsalicylate in Oil (0.13 Gm per cc) with Chlorobutanol 3%** 15 cc 30 cc 60 cc and 120 cc vials and 480 cc bottle  
oil containing subsalicylate w

**Bismuth Subsalicylate in Oil (0.2 Gm per cc) with Chlorobutanol 3%** 15 cc 30 cc 60 cc and 120 cc vials and 480 cc bottle A suspension of bismuth subsalicylate in vegetable oil containing in each cubic centimeter 0.2 Gm of bismuth subsalicylate with 3 per cent of chlorobutanol added

**THE LAKESIDE LABORATORIES, INC**

**Ampuls Bismuth Subsalicylate in Oil with Chlorobutanol 1 cc** Each cubic centimeter contains bismuth subsalicylate 0.13 Gm suspended in neutral vegetable oil with 3 per cent chlorobutanol

**Bismuth Subsalicylate with Chlorobutanol 30 cc and 60 cc vials** Each cubic centimeter contains bismuth subsalicylate 0.13 Gm suspended in neutral vegetable oil with 3 per cent chlorobutanol

**MERCK & Co INC**

**Bismuth Subsalicylate (Powder)** bulk

**PARKE, DAVIS & COMPANY**

**Bismuth Salicylate in Oil 30 cc, 60 cc, and 500 cc bottles** A suspension of bismuth subsalicylate in olive oil containing 3 per cent of chlorobutanol Each cubic centimeter contains bismuth subsalicylate 0.13 Gm

**Glaseptic Ampules Bismuth Salicylate in Oil 0.13 Gm in 1 cc** Each ampul contains 1 cc of a suspension of bismuth subsalicylate 0.13 Gm in olive oil containing 3 per cent of chlorobutanol

**SHARP & DOHME INC**

**Bismuth Subsalicylate with Chlorobutanol 3%, in Oil 1 cc 30 cc 100 cc and 500 cc** A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate 0.13 Gm with 3 per cent of chlorobutanol added

of bismuth concentration in the body. An adequate amount of sobisminol mass by mouth can be expected to result in a curve for urinary excretion resembling closely in course and degree those given by intramuscular injection of the water soluble and oil soluble compounds. The oral dose has to be considerably higher than the i.m.

... continues for many days.

The toxicity of sobisminol compares favorably with that of other water soluble bismuth compounds used in the treatment of syphilis. Side effects appear to be usually of a relatively transient nature. They include nausea, vomiting, burning sensations in the esophagus, diarrhea, stomatitis and bismuth line. There appears to be no tendency to cumulative toxic effects.

**Dosage.**—Adult dosage, from two to three capsules three times a day, taken with plenty of water, at 10 a. m., 3 p. m. and 8 p. m. Each capsule represents 150 mg. of metallic bismuth. Unless contraindications arise, such therapy may be continued for from ten to twelve weeks and represents a course of bismuth therapy. For children the dosage may be cut down to one capsule three times a day, or a 75 mg. capsule three times a day for a young child.

### Tests and Standards.—

Sobisminol mass occurs as a red brown to chocolate brown colored pasty mass, possessing an odor similar to that of bismuth, a bitter taste, with a ... and alcohol, partial ... tion made by disso- ... water to make a volume of 10 cc. should not be above 119 as determined with a glass electrode.

Dissolve 1 Gm. of sobisminol mass in 10 cc. of water and halve the solution; to one portion add 5 cc. of 0.5 per cent sodium bicarbonate solution; to the other portion add 5 cc. of 0.1 per cent hydrochloric acid. Neither solution yields a precipitate within fifteen minutes.

Dissolve 2 Gm. of sobisminol mass in 100 cc. of water; boil a 5 cc. portion: the solution remains clear and unchanged. To a separate portion of 1 cc. add 10 cc. of water and 1 cc. of 5 per cent sodium iodide solution: the solution remains clear. To another 1 cc. portion add 1 cc. of diluted hydrochloric acid, 5 cc. of water and 5 cc. of hydrogen sulfide solution: a black precipitate forms; to another 1 cc. portion add 3 cc. of diluted sulfuric acid and 1 cc. of 5 per cent sodium iodide solution: a red precipitate forms. To a 20 cc. portion add 2 cc. of nitric acid, adding more nitric acid dropwise, if necessary, until the solution is clear; divide into two equal parts; retain one part as a control and add 2 cc. of silver nitrate solution to the other part; when compared with the control, not more than a trace of turbidity is apparent (chloride). To another 20 cc. portion add 2 cc. of hydrochloric acid, adding more hydrochloric acid dropwise, if necessary, until the solution is clear; divide into two equal parts, retain one part as a control and add 2 cc.

...ed in Methods of Analysis  
Chemists fourth edition,  
add 0.1 Gm of anhydrous  
a period of two and one  
The amount of nitrogen  
is not less than 3.60 per cent nor more than 4.40 per cent

Dissolve about 0.6 Gm of solisminol mass, accurately weighed in  
100 cc of water and rapidly add 8 cc of concentrated nitric acid. Add  
water until the  
boiling and  
diammonium  
with boiling  
Collect the  
supernatant  
liquid, then wash the precipitate by decantation with four 50 cc por-  
tions of hot water, passing these washings through the crucible, and  
finally complete the transfer of the precipitate by means of cold water.  
Dry the crucible and contents at 110 C for one hour, suspend the  
a minutes  
is heated  
he ignited  
conversion  
found for  
per cent

**PROPYLENE GLYCOL.** The propylene glycol used in the preparation of  
solisminol mass and solisminol solution conforms to the New and Non  
official Remedies standards for this substance, which see

**SODIUM BISMUTHATE.** The sodium bismuthate used in the preparation  
of solisminol mass and solisminol solution conforms to the following tests  
for identity and purity

Sodium bismuthate occurs as a nearly odorless yellow brown powder  
containing not less than 80 per cent of  $\text{NaBiO}_4$ .

Dissolve 1 Gm of sodium bismuthate in a mixture of 5 cc. of hydro-  
chloric acid and 15 cc of water a slightly turbid yellow solution  
results. Agitate 2 Gm of sodium bismuthate with 50 cc of water fre-  
quently during one hour the resultant suspension is alkaline to  
phenolphthalein, filter, rejecting the first few cubic centimeters  
evaporate 25 cc of the clear filtrate in a tared dish, dry the residue at  
120 C and weigh the weight of the residue is not more than 0.003 Gm.

Boil 2.5 Gm of sodium bismuthate and 40 cc of water for ten  
minutes, cool, dilute to 50 cc with water, mix well, filter and divide  
into 10 cc portions, to one portion add 0.5 cc of nitric acid and 1 cc

Heat 0.5 Gm of sodium bismuthate with 5 cc of nitric acid until  
fumes of sulfur trioxide appear, then complete the test for arsenic  
according to the method described in the U. S. P. XI. The arsenic  
content should not exceed 2 parts per million.

Dissolve about 0.25 Gm of sodium bismuthate, accurately weighed, in  
8 cc of nitric acid, dilute with 100 cc of water, and continue the assay  
for bismuth as directed under solisminol mass the amount of bismuth  
found corresponds to not less than 66.5 per cent nor more than 72.5  
per cent.

...ately weighed, to  
flask,  
e the  
ition  
 $\text{BiO}_3$   
and





*in proportion* Generally a series of from twenty to twenty-five injections is considered a course of treatment. In cases of arsenical sensitization the bismuth injections may be continued for a much longer period.

### Tests and Standards—

Sobisminol solution occurs as a clear dark brown red colored liquid possessing an odor similar to *trisopropanolamine* and a sweet, mildly metallic taste. It is miscible with an equal volume of water or alcohol.

The pH of a portion of sobisminol solution is not below 11.1 nor above 11.5 as determined by means of a glass electrode. The specific gravity of sobisminol solution is not less than 1.064 nor more than 1.066 at 25 C.

Undiluted sobisminol solution responds to the tests for identity and purity stated under sobisminol mass.

Transfer 5 cc of sobisminol solution, accurately measured, to a 500 cc Leaker and determine the bismuth content according to the method stated under sobisminol mass (the amount of bismuth found is not less than 0.0195 Gm nor more than 0.0205 Gm per cubic centimeter).

Transfer 5 cc of sobisminol solution, accurately measured, to a 500 cc Kjeldahl flask and determine the nitrogen content according to the method stated under sobisminol mass (the amount of nitrogen found is not less than 0.0054 Gm nor more than 0.0060 Gm per cubic centimeter).

The propylene glycol, sodium bismuthate and *trisopropanolamine* used in the preparation of sobisminol solution corresponds to the standards for these substances as indicated under sobisminol mass.

Sobisminol Solution is manufactured by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938, expires 1955).

### CUTTER LABORATORIES

Ampoules Sobisminol Solution. 1 cc and 2 cc

Sobisminol Solution: 50 cc bottles

### ELI LILLY AND COMPANY

Ampoules Sobisminol Solution 1 cc, 2 cc, and 50 cc

### E. R. SQUIBB & SONS

Sobisminol Solution: 50 cc bottle

Ampuls Sobisminol Solution: 50 cc

**SODIUM IODOBISMUTHITE**—Sodium bismuth iodide.—A compound formed by the interaction of bismuth chloride and sodium iodide in ethyl acetate solution, consisting essentially of hydrated sodium iodobismuthite (sodium bismuth iodide)  $\text{Na}_2\text{BiI}_6$ , with inorganic salts. It contains approximately 21 per cent bismuth (Bi), 62 per cent iodide (I) and 11 per cent water of hydration.

*Actions and Uses*—It is claimed for sodium iodobismuthite that it has the quality of appearing in the spinal fluid and of penetrating the brain tissue. This claim and therapeutic indications based upon it require further confirmation.

*Dosage*—See Iodobismutol with Saligenin.

*Tests and Standards.*—

Sodium iodobismuthite occurs as a red crystalline compound, odorless, or having only a faint acetic or ethyl acetate odor, permanent in dry air and possessing an astringent taste. It yields a clear solution with one part water; on moderate dilution of the solution, sodium iodobismuthite hydrolyzes to form a black precipitate of bismuth iodide in a finely divided state, while on further addition of water the black precipitate changes to red bismuth oxyiodide. Hydrolysis may be retarded by the addition of acids or alkali iodides. The aqueous solution is neutral or faintly acid to litmus. Sodium iodobismuthite dissolves readily and without decomposition in ethylene-glycol, propylene glycol, glycerin, anhydrous alcohol and ethyl acetate; it is insoluble in absolute ether, chloroform, carbon disulfide, petroleum ether, fixed oils and liquid petrolatum. On heating the product in an oven at 80 to 110 C., it loses water of hydration, with slight decomposition, leaving a maroon colored residue that becomes brown or black on aging, and that changes to red on exposure to moisture.

Add 3 cc. of hydrochloric acid and 25 cc. of water to about 0.5 Gm. of sodium iodobismuthite, add an excess of stronger ammonia water, filter and wash the filter with water. Ignite the filter in a quartz crucible; the residue is yellow. A few drops of the filtrate imparts an intense yellow color to a nonluminous flame. Add 3 cc. of ferric chloride solution to a 10 cc. portion of the filtrate acidified with hydrochloric acid, shake with 3 cc. of chloroform; a violet coloration is imparted to the chloroform. Add 5 cc. of chloroform to about 0.2 Gm. of sodium iodobismuthite and shake the mixture; the chloroform remains clear and colorless (*free iodine and distinction from guinine bismuth iodide*). Percolate 0.1 Gm. of sodium iodobismuthite with 10 cc. of absolute ether; no residue remains after the evaporation of the solvent. Add 2 cc. of nitric acid to 1.5 Gm. of sodium iodobismuthite in a quartz dish, evaporate on a steam bath and ignite at red heat; dissolve in 5 cc. of hydrochloric acid, the solution meets the requirements of the Dettendorff test, U. S. P. X (*arsenic*). Add just sufficient nitric acid to blacken 3 Gm. of sodium iodobismuthite contained in a 150 cc. beaker, add 100 cc. of water and boil; filter and evaporate the filtrate to 30 cc., filter again and divide the latter filtrate into portions of 5 cc. each. Mix one portion with an equal volume of dilute sulfuric acid; the liquid does not become cloudy (*lead*); precipitate another portion with a slight excess of ammonia water; the supernatant liquid does not exhibit a bluish tint (*copper*); another portion is not immediately affected by barium nitrate solution (*sulfate*). To another portion, add diluted hydrochloric acid; no precipitate is formed which is insoluble in a slight excess of hydrochloric acid, but soluble in ammonia water (*silver*).

Transfer about 0.4 Gm. of sodium iodobismuthite, accurately weighed, to a wide mouth weighing bottle and heat to constant weight in an oven at 110 C.; the loss in weight is not less than 10.5 per cent nor more than 12.5 per cent.

Transfer about 0.2 Gm. of sodium iodobismuthite, accurately weighed, to a beaker, dissolve in 3 cc. of hydrochloric acid and 125 cc. of water saturate the solution with hydrogen sulfide to precipitate completely the bismuth as bismuth sulfide, filter in a gooch crucible, wash with water, alcohol, chloroform, and ether in this order, dry for one hour at 100 C., cool in a desiccator and weigh; repeat the washing with chloroform and ether and the drying at 100 C. until constant weight is attained; the bismuth sulfide weight is equivalent to not more than 21.8 per cent, nor less than 20.3 per cent bismuth.

Transfer about 0.2 Gm. of sodium iodobismuthite, accurately weighed, to a 250 cc. beaker, add 10 cc. of a solution of acid silver nitrate (prepared by dissolving 1 Gm. of silver nitrate in 20 cc. of water and adding 5 cc. of nitric acid) and then 100 cc. of water, allow to stand two hours, filter, using a filter paper, wash well with water. Without

allowing the precipitate to dry, puncture the filter and wash the precipitate into a 250 cc glass stoppered Erlenmeyer flask, using 100 cc of stronger ammonia water, agitate the solution, then allow the flask and contents to stand two hours collect the precipitate on a prepared gooch crucible and wash it with diluted ammonia water, then with water, dry to constant weight at 100 C. The weight of silver iodide is equivalent to not less than 60 per cent nor more than 63 per cent iodide. Add 10 cc of potassium iodide solution to the filtrate and heat on the steam bath until most of the ammonia has been removed filter the solution and collect the precipitate on a prepared gooch crucible, wash with water, dry to constant weight at 100 C, the weight of silver iodide is equivalent to not more than 0.7 per cent chloride.

### SODIUM POTASSIUM BISMUTHYL TARTRATE

—A basic water soluble sodium potassium bismuth tartrate containing from 40.75 to 41.25 per cent of bismuth.

*Actions and Uses*—Sodium potassium bismuthyl tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds).

#### Tests and Standards —

Sodium potassium bismuthyl tartrate is a white heavy powder soluble in water and insoluble in organic solvents.

During the ignition of about 0.1 Gm of sodium potassium bismuthyl tartrate in a quartz crucible a small globule of metallic bismuth forms that oxidizes on extended heating. The residue is yellow and alkaline to litmus, and effervesces with acids.

Transfer 0.1 Gm of sodium potassium bismuthyl tartrate to a test tube add 5 cc. of water and sufficient diluted hydrochloric acid to dissolve the precipitate first formed and add 0.5 cc. of barium chloride solution no cloudiness appears within 2 minutes.

Transfer 0.1 Gm of sodium potassium bismuthyl tartrate to a test tube add 5 cc of water and sufficient diluted nitric acid to dissolve the precipitate first formed and add 0.5 cc of silver nitrate solution no precipitate appears.

A sample of sodium potassium bismuthyl tartrate loses not more than 0.3 per cent of its weight when dried in a vacuum over sulfuric acid.

Transfer about 0.5 Gm of sodium potassium bismuthyl tartrate accurately weighed to an Erlenmeyer flask, add 100 cc of water, add diluted hydrochloric acid a drop at a time until the precipitate that forms redissolves saturate with hydrogen sulfide, filter, wash successively with water alcohol chloroform and ether dry at 100 C, cool in a desiccator and weigh the bismuth sulfide weighed is equivalent to not less than 40.75 per cent nor more than 41.25 per cent of bismuth.

**THIO-BISMOL**—Sodium bismuth thio glycolate—A salt formed by the interaction of sodium thio glycolate and bismuth hydroxide. The product has the general formula  $Bi_2(SCH_2CO_2Na)_3$ , though it may differ slightly in composition from this formula. It contains approximately 38 per cent of bismuth.

*Actions and Uses*—Thio bismol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of

syphilis (see preceding general article, Bismuth Compounds); it is a water-soluble compound, readily absorbable, and produces relatively little local injury. A single injection of 0.1 to 0.2 Gm has a definite effect in temporarily stopping the course of a therapeutic malaria.

*Dosage.*—For the average adult, 0.2 Gm. administered intramuscularly three times a week for a series of from twelve to fifteen doses

### *Tests and Standards.*—

Thio-bismol occurs as a canary yellow hygroscopic noncrystalline but granular substance possessing a garlic-like odor. It is freely soluble in water but the solutions are not stable.

Add 1 drop of diluted hydrochloric acid to 1 cc. of a 2 per cent solution of thio-bismol solution: a heavy yellow precipitate separates that dissolves on the addition of another drop of acid. Add several drops of acetic acid to 1 cc. of a 2 per cent solution of thio-bismol: no precipitate forms. Add 3 drops of ammonia water to 1 cc. of a 2 per cent solution: a slight change of color and a slight precipitate occurs within one half hour. Add 1 drop of sodium hydroxide solution to 1 cc. of a 2 per cent solution of thio-bismol: a precipitate forms, insoluble in excess of reagent. Add several drops of copper sulfate solution to 1 cc. of a 2 per cent solution of thio-bismol: a precipitate forms that gives the suspension a murky greenish brown appearance. The precipitate dissolves in sodium hydroxide solution, leaving a yellow solution

diluted hydrochloric acid to just dissolve the precipitate first formed, and add several drops of barium chloride solution; a precipitate does not appear.

Heat an accurately weighed sample of thio-bismol weighing about 1 Gm in a 100 C. oven for one hour, cool in a desiccator, and weigh: the sample does not lose more than 5 per cent in weight. Transfer an accurately weighed sample of thio-bismol weighing about 0.4 Gm to an Erlenmeyer flask, dissolve in 100 cc. of water, add enough diluted hydrochloric acid to just dissolve the precipitate first formed, saturate with hydrogen sulfide until the bismuth is completely precipitated as bismuth sulfide, collect the precipitate in a prepared Gooch crucible, wash with water, alcohol, ether, chloroform and ether in the order named, dry at 100 C., cool in a desiccator and weigh: the bismuth calculated from the bismuth sulfide is equivalent to not less than 37 per cent nor more than 39.5 per cent in the original calculated to the dry substance. Evaporate the filtrate from the bismuth determination to a small bulk, transfer to a platinum dish, add sulfuric acid and evaporate to dryness; add a few drops of sulfuric acid, evaporate to dryness again, volatilize a small amount of ammonium carbonate from the dish, cool in a desiccator and weigh: the sodium calculated from the weight of sodium sulfate is not less than 12.23 per cent nor more than 13.04 per cent in the original substance calculated to the dry substance.

PARKE, DAVIS & COMPANY

Ampoules Thio-Bismol: 0.2 Gm and 2 Gm

U S trademark 220,808

**Chiniofon**

**CHINIOFON**—*Pulvis Chiniofoni U S P XI*—Chiniofon Powder, U S P XI—"A mixture of 7 iodo 8 hydroxyquinoline 5 sulfonic acid its sodium salt, and sodium bicarbonate containing not less than 26.5 and not more than 29 per cent of iodine (I) U S P



For description and standards see the U S Pharmacopeia under Chiniofonum and Tabellae Chiniofoni

**Actions and Uses**—Chiniofon, which is closely similar to preparations introduced under various proprietary names as wound antiseptics has been found to be of use in the treatment of amebic dysentery. It is claimed that the action of the drug is probably due to its absorption and direct action through the blood stream on the amebas invading the bowel wall. The drug has been reported in some cases to produce diarrhea, but serious toxic effects do not appear to be common.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. It is important that negative findings should be checked by stool cultures.

In view of the frequency of persistent infection in the absence of marked symptoms adequate therapy includes reexaminations and repetitions of courses of treatment.

**Dosage**—Orally for adults from 0.25 to 1.0 Gm. in the form of pills, cachets or solution three times daily for children according to age rectally 1 to 5 Gm. freshly dissolved in 200 cc. of water at a temperature not exceeding 44° C. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute cases and in the more serious chronic cases accompanied by obstinate clinical symptoms. It has been pointed out that the iodine content of chiniofon should be considered when chronic enteric amebiasis is accompanied by thyroid disturbance.

Until more evidence becomes available chiniofon should be used with caution in cases with liver damage.

G. D. SENTER & Co

**Tablets Chiniofen Enteric Coated 0.26 Gm.** The tablets are coated with a mixture of magnesium stearate and shellac.

WINTHIROP CHEMICAL COMPANY, INC.

**Chiniofon (Powder):** bulk.

**Tablets Chiniofen:** 0.25 Gm    The tablets are coated with keratin.

### *Mercury Compounds*

Mercury has been employed in the treatment of disease since time immemorial. It was employed very early in the treatment of skin diseases, metallic mercury being used incorporated in various ointments with elaborate bases. Naturally, when syphilis was called to the attention of the early practitioners, it was to be expected that they would employ some of these mercurial ointments for treating the disease. Thus mercury inunctions were the first form of mercury employed in treating syphilis. Later, Mathioli used it internally in the form of red mercuric oxide. Still others tried pills of metallic mercury internally, and mercury salts in solutions were also extensively used, for example, van Swieten's sublimate solution. In the early part of the nineteenth century the yellow mercurous iodide tablet was suggested and used by Ricord and later by his celebrated pupil, Fournier. Jonathan Hutchinson introduced mercury with chalk in the latter half of the last century. This also had a great vogue over a period of time. Mercury fumigations were employed quite extensively in the eighteenth century, but were discarded because of their danger. The intramuscular and intravenous injections of mercury salts have been used only in the past fifty or sixty years. One now finds the oral method of administration to be rarely employed. It is often the cause of troublesome gastro-intestinal symptoms. The inunction method obviates the digestive disturbances. If this method is to be employed, it is necessary for the physician to instruct the patient to rub in the ointment vigorously for thirty minutes by the clock. Only the mercury that penetrates the hair follicles is absorbed. Simply placing the ointment on the outside of the skin is of little value. After rubbing it in for thirty minutes, it probably is permissible to remove the excess that is left on the skin by the use of soap and water, or even a small amount of benzine with a cloth. In using mercury inunctions, different sites should, if possible, be employed each night for at least six nights. As a rule, hairy persons do not stand inunctions well; there is a tendency to the development of folliculitis.

In more recent years the attempt to improve mercurial therapy has been mainly along two lines: the perfection of intramuscular usage and the introduction of the organic compounds.

The intramuscular injections are of two types, either of the soluble or of the insoluble salts. As a rule the soluble salts are somewhat more painful and because of their rapid absorption require an injection daily, or at least every other day. They are of great value in getting the patient under rapid mercurialization. For this same purpose one may also employ intra-

venous injections, though they are not used much in this country. Moreover, these preparations when given intravenously must be given daily if they are to do any good since mercury is so rapidly immobilized, and as a rule daily intravenous injections are scarcely practical. The most popular of the soluble salts are probably mercury bichloride red mercuric iodide and mercuric succinimide. Mercuric cyanide and mercuric oxycyanide are used considerably in France for intravenous administration.

The claim is made for the insoluble salts of mercury that they do not require administration so frequently and that they are less painful. True, there is danger of a certain amount of cumulative absorption so that it is necessary for the physician to watch the patient very closely when the insoluble salts are being employed. The difference between the mercurous and mercuric compounds is primarily one of solubility and absorption. After the mercurous compounds are absorbed, a process that is quite possibly preceded by their oxidation to mercuric compounds, no difference has been demonstrated. Of the insoluble or perhaps better, semisoluble salts, mercuric salicylate is probably the best and should be comparatively safe if the patient is observed carefully the injections required being given only once a week. They are quite painful.

In using mercury in the treatment of syphilis the physician should watch the patient carefully for symptoms of intoxication, for example stomatitis gastro intestinal symptoms or symptoms of irritation of the kidneys. Moreover the use of bismuth as an antisyphilitic agent has replaced that of mercury.

**MERCURETTES** — *Tabellae Hydrargyri eum Oleo Theobromatis* — Briquettes each containing finely divided metallic mercury 3.25 Gm incorporated with theobroma (cacao butter) and perfumed. Each briquette weighs 6 Gm.

**Actions and Uses** — The same as those of strong mercurial ointment. It is claimed that in the treatment of syphilis and certain forms of parasitic skin diseases where ointment of mercury has been employed the use of mercurettes permits a more accurate dosage and is more convenient and less disagreeable.

**Dosage** — Applied byunction. If less than one briquette is to be used, it may be divided by cutting with a knife.

**PARKE, DAVIS & COMPANY**

**Mercurettes**

U. S. trademark 180 215

**MERCURIC SALICYLATE** — Contains the equivalent of not less than 54 per cent and not more than 57.5 per cent of  $Hg^{+2}$ . U. S. P.

For description and standards see the U. S. Pharmacopeia under *Hydrargyri Salicylas* and *Injectio Hydrargyri Salicylatis*.

**Actions and Uses** — Mercuric salicylate is used by intramuscular injection in the treatment of syphilis.



## CHIEPLIN BIOLOGICAL LABORATORIES, INC.

**Ampule Mercuric Salicylate Suspended in Oil:** 1 cc. Each cubic centimeter contains mercuric salicylate 0.065 Gm quinine and urea hydrochloride 0.005 Gm., wool fat 0.1 Gm., distilled water 0.05 cc. and Wesson oil (maize oil) to make 1 cc.

**Mercuric Salicylate Suspended in Oil:** 60 cc. bottles Each cubic centimeter contains mercuric salicylate 0.065 Gm quinine and urea hydrochloride 0.005 Gm., wool fat 0.1 Gm., distilled water 0.05 cc. and Wesson oil (maize oil) to make 1 cc

## THE LAKESIDE LABORATORIES, INC.

**Ampul Solution Mercuric Salicylate (in oil):** 0.065 Gm., 0.097 Gm., 0.13 Gm. in 1 cc. Each ampul contains mercuric salicylate U. S. P. suspended in vegetable oil containing 3 per cent chlorobutanol.

## THE Wm. S. MERRELL COMPANY

**Ampul Mercury Salicylate in Oil:** 1 cc. Each cubic centimeter contains mercuric salicylate 0.065 Gm. in sterile olive oil suspension containing 0.5 per cent quinine and urea hydrochloride-U. S. P.

**Ampul Mercury Salicylate in Oil:** 1 cc. Each cubic centimeter contains mercuric salicylate 0.1 Gm in sterile olive oil suspension containing 0.5 per cent quinine and urea hydrochloride-U. S. P.

## PARKE, DAVIS &amp; COMPANY

**Glaseptic Ampoule Mercury Salicylate in Oil:** 1 cc. Each cubic centimeter contains mercuric salicylate 0.065 Gm.; apothesine, 0.01 Gm.; in olive oil.

**MERCURIC SUCCINIMIDE.**—"When dried over sulfuric acid for 18 hours, contains not less than 49.5 per cent and not more than 51 per cent of Hg, corresponding to not less than 98 per cent of  $C_6H_5N_2O.Hg$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under Hydrargyri Succinimidum and the National Formulary under Ampullae Hydrargyri Succinimidi.

**Actions and Uses.**—Mercuric succinimide has the action of other salts of mercury, but its solutions are said to be relatively nonirritating. The preparation is used as are other compounds of mercury in the treatment of syphilis.

**Dosage.**—Mercuric succinimide is used mainly by intramuscular injection. The daily dose is from 0.01 to 0.02 Gm. given in the form of a 2.5 per cent solution (from 0.5 to 1 cc. of such solution). Mercuric succinimide may be given by the mouth in doses of from 0.01 to 0.015 Gm.

ABBOTT LABORATORIES

Ampoule Solution Mercury Succinimide 1 cc Mercuric succinimide 0.01 Gm in water

CHEPLIN BIOLOGICAL LABORATORIES, INC

Ampule Solution Mercuric Succinimide, 1%, 1 cc Mercuric succinimide 0.01 Gm, benzyl alcohol 0.01 cc, and glycerin 0.013 Gm in sufficient distilled water to make 1 cc

Solution Mercuric Succinimide, 1%, 30 cc vials Each 1 cc contains 0.01 Gm of mercuric succinimide 0.01 cc of benzyl alcohol and 0.013 Gm of glycerin

Ampule Solution Mercuric Succinimide, 2%, 1 cc Each 1 cc contains 0.02 Gm of mercuric succinimide, 0.01 cc of benzyl alcohol and 0.013 Gm of glycerin

Solution Mercuric Succinimide, 2%, 30 cc vials Each 1 cc contains 0.02 Gm of mercuric succinimide 0.01 cc of benzyl alcohol and 0.013 Gm of glycerin

LYND PRODUCTS, INC

Ampoule Solution Mercury Succinimide 1 cc Mercuric succinimide 0.01 Gm per cc

FRINT, EATON & COMPANY

Ampul Solution Mercuric Succinimide, 1%, 1 cc

THE LAKESIDE LABORATORIES, INC

Ampoule Solution Mercury Succinimide 1 cc Mercuric succinimide 0.01 Gm in distilled water to make 1 cc

MERCK & CO, INC

Mercuric Succinimide (*Powder*) bulk

THE WM S MERRILL COMPANY

Ampule Solution Mercury Succinimide 1 cc Mercuric succinimide 0.01 Gm per cc

PARKER, DAVIS & COMPANY

Glaseptic Ampoule Solution Mercury Succinimide 1 cc Each cubic centimeter contains mercuric succinimide 0.01 Gm apothecary 0.005 Gm in distilled water

SHARP & DOWNEY, INC

Ampul Solution Mercury Succinimide 0.01 Gm in 1 cc Benzyl alcohol 11 per cent is added as a local anesthetic glycerin 0.013 Gm per cc is added for purposes of viscosity

**SOLUTION COLLOIDAL MERCURY SULFIDE-HILLE.**—*Liquor Hydrargyri Sulfidi Colloidalis.*—*Solution Colloidal Mercuric Sulfide Solution Mersulfol.*—A colloidal 2 per cent solution of mercuric sulfide in water, stabilized with a hydrolyzed protein substance and preserved with 0.2 per cent of tricresol.

*Actions and Uses.*—Solution colloidal mercury sulfide-Hille is proposed for intramuscular injection in the treatment of syphilis.

*Dosage.*—The usual dose is from 2 to 3 cc. administered intramuscularly twice a week for a course of sixteen to twenty injections. With intermittent treatment there should then be a rest period of six or eight weeks. If continuous therapy is being used, of course some other antisyphilitic, for example arsphenamine, might then be employed.

#### *Tests and Standards.*—

Solution colloidal mercury sulfide-Hille is black in reflected light and brown in transmitted light. It possesses the odor and taste of cresol. It has a specific gravity of from 1.0670 to 1.0690.

Solution colloidal mercury sulfide-Hille is neutral to litmus (Place a drop of the solution over a piece of blue litmus paper and a drop on red litmus paper; after one minute the original color can be detected on the edges of the drop.) To 1 cc. of the original solution add 3 cc. of iodine solution; a clear reddish solution results which within an hour becomes turbid because of the separation of a red precipitate.

To 20 cc. of solution colloidal mercury sulfide-Hille add 7 Gm. of sodium chloride and boil until the colloid coagulates, filter off the precipitate and cool the solution; the yellowish solution remains clear (lead), dilute the filtrate to 25 cc. Transfer about one fourth of the black precipitate to a beaker, add 10 cc. of water, 2 cc. of diluted hydrochloric acid and a small crystal of potassium chlorate, boil until the solution no longer evolves chlorine, filter off the sulfur and add a few drops of stannous chloride; a white precipitate that changes to gray forms. To 5 cc. of the yellowish filtrate add 5 cc. of ammonia water; no color change occurs (copper) and no precipitate forms (bismuth, iron). To 5 cc. of the filtrate, add 1 cc. of a 1 per cent solution of tannic acid; a white precipitate forms. To 5 cc. of the filtrate add 2 drops of a 36 per cent solution of acetic acid; a turbidity appears that disappears on the addition of more acetic acid. To 5 cc. of the filtrate add 1 cc. of copper sulfate solution; a slight precipitate forms that is rendered soluble by adding 2 volumes of water, add 1 cc. of normal sodium hydroxide solution; a violet color appears. To 5 cc. of the filtrate add 1 cc. of mercuric chloride solution; no precipitate forms. To 5 cc. of the original solution add 5 cc. of diluted hydrochloric acid and a small crystal of potassium chlorate and heat. When the black precipitate has disappeared, filter and boil to a small volume. Add 2 cc. of sulfuric acid and continue the boiling until sulfur dioxide is no longer given off; cool: this solution conforms to the U. S. P. test for arsenic.

Transfer exactly 3 cc. of solution colloidal mercury sulfide-Hille to a weighed platinum dish, add sodium sulfide solution (50 Gm. sodium sulfide dissolved to make 100 cc.) until the precipitate just dissolves and then add as much again, electrolyze the solution for six hours using 6 volts, wash with water, alcohol and ether, dry in a desiccator containing sulfuric acid and a beaker containing metallic mercury, weigh; the mercury calculated to mercuric sulfide is not less than 1.94 per cent nor more than 2.06 per cent.

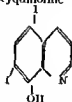
## HILLE LABORATORIES

Solution Colloidal Mercury Sulfide bulk

## Iodine Compounds

**DIODOQUIN**—57 Diodo 8 hydroxyquinoline  $C_8H_6N_2O$ 

I —A compound resulting from the introduction of two atoms of iodine into 8 hydroxyquinoline



**Actions and Uses**—Diodoquin is proposed as an antiprotozoan agent for use in amebic dysentery and in the treatment of *Trichomonas hominis* (intestinalis) infections

**Dosage**—Adults—seven to ten tablets a day for fifteen to twenty days

**Tests and Standards**—

Diodoquin occurs as a yellowish brown practically odorless powder. It is almost insoluble in water, sparingly soluble in alcohol, ether and acetone, soluble in hot pyridine and in hot dioxane. Diodoquin melts between 200 and 215 C with extensive decomposition.

Warm a few crystals of diodoquin with 1 cc of concentrated sulfuric acid, vapors of iodine are evolved. Heat 0.5 Gm of diodoquin mixed with 5 Gm of anhydrous sodium carbonate in a deep crucible, cool, extract the mixture in 10 cc of water and filter with diluted nitric acid. Filter and add 13 cc of tenth normal silver nitrate solution to the filtrate. Shake to coagulate the precipitate and filter. Add 1 cc of tenth normal silver nitrate solution to the filtrate, shake and filter through a fresh filter paper. Wash the precipitate on the filter, a yellow color is observed (distinction from vioform which gives a white precipitate).

Dry 1 Gm of diodoquin over phosphorus pentoxide for twenty-four hours; the loss in weight is less than 0.1 per cent.

Incinerate about 1 Gm of diodoquin; the ash is not over 0.5 per cent.

Mix about 0.15 Gm of diodoquin accurately weighed in a nickel crucible with 5 Gm of anhydrous potassium carbonate (or sodium carbonate). Mix thoroughly with a dry stirring rod, settle the mixture by tapping the crucible, overlay with 5 Gm of potassium carbonate (or sodium carbonate) and ignite at about 600 C for from three to five minutes. Cool, transfer the crucible to a 500 cc wide mouth conical flask and extract with about 20 cc of distilled water. Acidify the solution carefully dropwise with five normal hydrochloric acid (about 30 cc). Filter the solution quantitatively into a 250 cc glass stoppered flask using two 70 cc portions of water to rinse the flask and filter paper. The volume at this point should be about 100 cc. Add a cooled mixture of 35 cc of hydrochloric acid, 35 cc of distilled water and add 10 cc of purified chloroform. Titrate with tenth normal potassium iodate to the disappearance of pink color in the chloroform layer (add iodate solution dropwise and shake vigorously near the endpoint). One cc of tenth normal potassium iodate solution is equivalent to 0.00423 Gm of iodine. Diodoquin contains not less than 60.5 per cent nor more than 64.0 per cent of iodine.

G. D. SEARLE &amp; Co.

Tablets Diodoquin: 0.21 Gm.

U. S. Trademark No. 336,484

*Quinine Derivatives*

The action of quinine is essentially the same in all its compounds. The official salts have the disadvantage of the bitter taste, and of producing a local action on the stomach and other tissues. To obviate these difficulties, insoluble compounds like the alkaloid or the tannate have been used, since these pass the mouth and stomach without offending the taste or disturbing the stomach. The same object is obtained more or less completely in a number of synthetic compounds in which the quinine radical is combined with other radicals, such as those of carbonic acid, to form insoluble, and therefore tasteless, esters. In the intestines these esters are broken up more or less rapidly into the alkaloid quinine and the other components. The rapidity with which this decomposition occurs will determine to a large extent the intensity of the therapeutic effect and the liability to produce cinchonism. Where oral medication is not feasible quinine derivatives may be administered by intravenous injection, but this should be reserved for emergency cases of severe malarial infection and with due cognizance that this route of administration may produce a marked fall in blood pressure. For such use, solutions of quinine salts should be diluted to a concentration not greater than 0.5 per cent and should be injected very slowly. The subcutaneous or intramuscular routes should not be employed because of the danger of local tissue damage. In those rare cases where neither oral nor intravenous administration is possible, the use of other antimalarial drugs should be resorted to.

Some of the esters also contain other therapeutically active radicals (phenetidin, salicyl, etc.). When liberated these produce their characteristic effects; but it is doubtful whether the combinations of several therapeutically active radicals in fixed proportions are superior to simple mixtures of the ingredients.

Totaquine, U. S. P., which is a mixture of alkaloids from the  
 . . . . . not less than 70 per cent  
 . . . . . developed for use  
 . . . . . as quinine com-

pounds

**QUININE DIHYDROCHLORIDE.** — "The dihydrochloride of an alkaloid obtained from cinchona." U. S. P.

For description and standards see the U. S. Pharmacopœia under *Quininae Dihydrochloridum* and the National Formulary under *Ampullae Quininae Dihydrochloridi*

*Actions and Uses.*—Quinine Dihydrochloride is similar to those of quinine, over which it has the same effects, being

more soluble in water. It is used where aqueous solutions of quinine are desired for intravenous injection in those cases of severe malarial infection where oral medication is not feasible. It should not be administered by subcutaneous or intramuscular injection because of the danger of local tissue damage. The absorption of intramuscular injections of quinine salts is slower than that following oral administration. Solutions of quinine dihydrochloride for intravenous administration should be diluted to a concentration not greater than 0.5 per cent and should be given slowly and with due cognizance of the danger of a serious fall in blood pressure, particularly in patients with cardiovascular impairment.

*Dosage*—From 0.24 to 0.65 Gm suitably diluted is given intravenously as indicated by the severity of the symptoms and the age of the patient. The dose of 0.65 Gm should not be repeated more than three times in twenty-four hours. Oral administration should be resumed as early as possible.

ENDO PRODUCTS, INC., RICHMOND HILL, N. Y.

Ampuls Solution Quinine Dihydrochloride 0.25 Gm in 1 cc, 0.5 Gm in 1 cc, 1.0 Gm in 2 cc. Each ampul contains the stated amount of quinine dihydrochloride dissolved in distilled water.

THE LAKESIDE LABORATORIES, INC.

Ampuls Solution Quinine Dihydrochloride 0.24 Gm in 1 cc, 0.49 Gm in 1 cc, 1.0 Gm in 2 cc (For Intravenous Use). Each ampul contains the stated amount of quinine dihydrochloride dissolved in distilled water.

Ampuls Solution Quinine Dihydrochloride 0.32 Gm in 5 cc, 0.49 Gm in 5 cc, 0.49 Gm in 10 cc, 0.65 Gm in 20 cc (For Intravenous Use). Each ampul contains the stated amount of quinine dihydrochloride dissolved in distilled water.

**QUININE DIHYDROCHLORIDE AND URETHANE**—A sterile aqueous solution containing quinine dihydrochloride U. S. P. 127 Gm and ethyl carbamate N. F. 6.65 Gm in each hundred cubic centimeters.

For standards see U. S. Pharmacopeia under Quininae Dihydrochloridum and the National Formulary under Aethylis Carbama.

*Actions and Uses*—A mixture of quinine dihydrochloride and urethane in aqueous solution is used as a sclerosing agent for injection in the obliterative treatment of varicose veins. The mixture is claimed to have antiseptic qualities. It should not be employed during menstruation, pregnancy, nor in the presence of heart disease, nephritis, diabetes, upper respiratory infection, or septic tonsillitis. It is contraindicated in the presence of phlebitis, suppurative ulceration, and incompetence of deep veins.

*Dosage.*—The initial injection should be limited to 0.5 cc. to determine whether idiosyncrasy exists; average amount for injection at any one site is 1 cc. and should not exceed 2 cc. The total quantity to be injected at a single sitting should not exceed 5 cc. to avoid the production of cinchonism. The injection should be made slowly to avoid dangerous consequences.

THE LAKESIDE LABORATORIES, INC.

Ampule Solution Quinine Dihydrochloride and Urethane: 2 cc. Each ampul contains quinine dihydrochloride 0.255 Gm and urethane 0.133 Gm.

**QUININE ETHYLCARBONATE.**—*Euquinine.*—“The ethylcarbonate of an alkaloid obtained from cinchona.” U. S. P.

For description and standards see the U. S. Pharmacopeia under *Quininae Aethylcarbonas*.

*Actions and Uses.*—Quinine ethylcarbonate is used in place of quinine sulfate and similar soluble quinine salts when a practically tasteless quinine compound is preferred.

*Dosage*—1 Gm.

MALLINCKRODT CHEMICAL WORKS

Quinine Ethyl Carbonate (*Powder*): bulk

MERCK & CO., INC.

Quinine Ethyl Carbonate (*Powder*): bulk.

**QUININE SULFATE.**—“The sulfate of an alkaloid obtained from cinchona” U. S. P.

For description and standards see the U. S. Pharmacopeia under *Quininae Sulfas*.

ELI LILLY AND COMPANY

*Coco-Quinine:* Each 100 cc. contains quinine sulfate, 2.19 Gm. suspended in a syrup flavored with chocolate, yerba santa and vanilla, and containing sodium benzoate 0.18 Gm per 100 cc., and alcohol 4 per cent

U. S. trademark 174,144

### Anthelmintic Agents

**CARBON TETRACHLORIDE**—U. S. P. Tetrachloromethane.

For description and standards see the U. S. Pharmacopeia under *Carbonei Tetrachloridum* and *Capsulae Carbonei Tetrachloridi*.

*Actions and Uses.*—Carbon tetrachloride has narcotic and anesthetic properties somewhat similar to those of chloroform. It has recently come into use as a vermifuge in the treatment of hookworm disease. It is reported that usually about 95 per

cent of the hookworms are removed by the first dose of carbon tetrachloride and that occasionally all are removed. As a vermifuge it appears to be relatively safe, but serious symptoms and even death have occurred, especially in patients addicted to the use of alcohol. During treatment some of the patients complain of headache. Good results are obtained by administration in water or milk or in gelatin capsules on an empty stomach followed in three hours by a purgative dose of magnesium sulfate. The capsules may be prepared extemporaneously. Lambert recommends giving the vermicide and a solution of magnesium sulfate together, claiming that this prevents headache. A mild laxative is generally given to constipated patients on the day previous to removal of the hookworms. (45 minims) may be given. Carbon tetrachloride should not be given with food. It should not be given during treatment.

**Dosage**—From 2 to 3 cc. For children 0.13 cc. for each year of age up to 15 years. If the drug is to be given with the purgative the dose for adults is administered in 50 cc. of a solution of magnesium sulfate. For children the dose of the purgative is appropriately reduced. The dose of 3 cc. should not be exceeded.

MERC & Co., Inc.

Carbon Tetrachloride (*Liquid*) bulk

PARKE DAVIS & COMPANY

Capsules Carbon Tetrachloride (*For Human Use*)  
12 cc

**TETRACHLOROETHYLENE** — Perchloroethylene — Ethylene Tetrachloride — Contains not less than 99 per cent and not more than 99.5 per cent of  $C_2Cl_4$ , the remainder consisting of alcohol. U. S. P.

For description and standards see the U. S. Pharmacopeia under Tetrachloroethylenum.

**Actions and Uses**—Observations of many workers have shown that tetrachlorethylene is a useful anthelmintic for the treatment of hookworm infestation. It has been used against other worms with less success although there is some evidence that it is useful in *Trichuris* infestation. It may be lethal to *Ascaris* but its use in that infestation is not advised because of the danger of causing migration of the worms. It is the consensus of the investigators that tetrachlorethylene is less toxic than carbon tetrachloride ( $CCl_4$ ) and at least as efficacious as the latter drug. It has a further advantage over carbon tetrachloride in that it does not raise the guanidine content of the



blood, which is important in cases exhibiting a calcium deficiency. Untoward reactions are rare, but giddiness, vomiting and drowsiness have been reported in some cases. It is probably better to keep the patient (especially children) in bed during the treatment.

*Dosage.*—From 1 to 3 cc., depending on the age of the patient. Tetrachlorethylene is usually given in soft gelatin capsules but has also been administered to children on a bit of sugar. The gastro-intestinal tract should be thoroughly emptied before administering tetrachlorethylene. Fats and alcohol must be avoided, because they favor absorption of the drug. A dose of tetrachlorethylene should be followed by a cathartic of sodium or magnesium sulfate. One dose usually suffices, but if necessary it may be repeated once after 2 or 3 days or from ten days to two weeks.

*NOTE.*—Broken capsules should be discarded; they should never be employed if it has been exposed to light for more than a very brief time, because of the phosgene formation by decomposition.

## CHAPTER V

# ASTRINGENTS AND CAUSTICS

### Aluminum Salts

Several of the compounds of aluminum are official including the ordinary alum or alumen U S P Aluminum acetate and aluminum subacetate are used in the form of solutions and are described in the National Formulary as Solution of Aluminum Acetate and Solution of Aluminum Subacetate

The aluminum compounds are used for their astringent action Since they are but little absorbed they are relatively nontoxic

Compounds of aluminum are astringent because of their property of precipitating albumin The exsiccated alum is more energetic not only because it contains a larger proportion of alum than the crystalline form but because it absorbs water from the tissue at the same time The acetate is milder than the sulfate as is usual with metallic salts

The aluminum compounds are not so astringent as the corresponding lead salts but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the exsiccated (burnt) alum When swallowed in over doses in such concentrated form they may cause gastritis and diarrhea Alum is sometimes used as an emetic

The aluminum compounds are slightly antiseptic a property which goes with their astringency Some of the organic compounds are said to be more actively antiseptic than the inorganic ones

Several proprietary preparations consisting of aluminum combined with organic acids have been introduced with a view to utilizing the astringent and antiseptic properties of their components Many of these possess no special advantages and have fallen into disuse or have been largely replaced by others of a more or less similar nature

Aluminum compounds in the form of gels used as antacids are described in the chapter on Gastrointestinal Drugs

### Copper Salts

#### COPPER CITRATE—Cupri Citras—Cupric Citrate—

The cupric salt of citric acid containing from 34 to 36 per cent of copper

*Actions Uses and Dosage*—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility

It may be used for the same purposes as and in doses similar to those of other salts of copper

blood, which is important in cases exhibiting a calcium deficiency. Untoward reactions are rare, but giddiness, vomiting and drowsiness have been reported in some cases. It is probably better to keep the patient (especially children) in bed during the treatment.

*Dosage.*—From 1 to 3 cc., depending on the age of the patient. Tetrachlorethylene is usually given in soft gelatin capsules but has also been administered to children on a lump of sugar. The gastro-intestinal tract should be thoroughly emptied before administering tetrachlorethylene. Fats and alcohol must be avoided, because they favor absorption of the drug. A dose of tetrachlorethylene should be followed by a saline cathartic of sodium or magnesium sulfate. One dose frequently suffices, but if necessary it may be repeated once after a period of from ten days to two weeks.

*NOTE.*—Broken capsules should be discarded; the solution should never be employed if it has been exposed to the air for more than a very brief time, because of the possibility of phosgene formation by decomposition.

## CHAPTER V

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Aluminum compounds in the form of gels used as antacids are described in the chapter on Gastrointestinal Drugs

#### Copper Salts

**COPPER CITRATE**—*Cupri Citras*—*Cupric Citrate*—The cupric salt of citric acid containing from 34 to 36 per cent of copper

*Actions Uses and Dosage*—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility

It may be used for the same purposes as and in doses similar to those of other salts of copper

*Tests and Standards—*

Copper citrate occurs as a green or bluish green, finely crystalline, odorless powder. It is slightly soluble in cold water; somewhat more soluble in a cold solution of an alkali citrate, forming a greenish-blue solution; more soluble in a hot solution of an alkali citrate, also soluble with decomposition in ammonia water and in mineral salts.

When dissolved in ammonia water, copper citrate yields an intense blue solution. When heated to 90 C., the salt loses water of hydration and assumes a pale blue color. At a higher temperature, it blackens and at a low red heat leaves a black residue of cupric oxide. If about 1 Gm of copper citrate is dissolved in 20 cc. of diluted hydrochloric acid, the solution diluted to 200 cc with hot water, the mixture saturated with hydrogen sulfide, filtered, and the filtrate evaporated nearly to dryness on the water bath, the residue responds to the usual tests for citric acid. If 0.5 Gm. of copper citrate is dissolved in 10 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution added, no immediate turbidity occurs. A solution of 0.5 Gm of the salt in 10 cc. of diluted sulfuric acid should not evolve any odor of acetic acid when boiled. The salt should be free from nitrates, chlorides and carbonates.

To about 0.5 Gm., accurately weighed, add 25 cc. water and 10 cc of normal sulfuric acid. Heat the mixture almost to boiling until solution is complete, adding a little more acid if necessary. Cool the solution and add 10 cc. of potassium iodide solution and allow it to stand five minutes, with occasional shaking. Add 200 cc. of water and titrate the liberated iodine with tenth normal sodium thiosulfate the titration should indicate not less than 21 per cent of copper.

**MALLINCKRODT CHEMICAL WORKS****Copper Citrate (Crystals): bulk.****MANHATTAN EYE SALVE COMPANY, INC.**

**Ophthalmic Ointment Copper Citrate 5 per Cent:** A sterile ointment containing copper citrate 5 per cent, wool fat 10 per cent, petrolatum 85 per cent, without alcohol or preservative.

**Ophthalmic Ointment Copper Citrate 10 per Cent:** A sterile ointment containing copper citrate 10 per cent, wool fat 10 per cent, petrolatum 80 per cent, without alcohol or preservative.

**Pyrogallol**

**LENIGALLOL.** — *Pyrogallolis Triacetat.* — Triacetyl pyrogallol  $C_6H_3(CH_3CO_2)_3$ . — Pyrogallol triacetate, obtained by replacing the hydroxyl groups of pyrogallol with acetate groups.

**Actions and Uses**—Lenigallol as such is said to be nonpoisonous and nonirritating, but it produces a mild and painless corrosive effect by the gradual liberation of pyrogallol.

It is used as a substitute for pyrogallol in psoriasis, lupus, acute and subacute eczema of children and other skin diseases.

**Dosage.**—In 5 to 10 per cent ointment, usually with zinc oxide

*Tests and Standards—*

Lenigallol is prepared by boiling 10 parts of pyrogallol 1 part sodium acetate and 25 parts of acetic anhydride for two hours and washing the crystalline product on a filter with water

It is a white crystalline powder melting at 165 C It is insoluble in water, but soluble with decomposition in warm aqueous alkalis

Lenigallol is incompatible with alkalis strong acids and oxidizing agents

**BILHUBER KNOLL CORP**

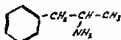
**Lenigallol-Zinc Ointment** Contains lenigallol 6 per cent in zinc oxide ointment U S P

## CHAPTER VI

### AUTONOMIC DRUGS

#### Sympathomimetic Agents

**AMPHETAMINE.**—Racemic Amphetamine.—Alpha-methylphenethylamine.—1-phenyl-2-aminopropane.—Benzedrine.—Racemic desoxynor-ephedrine.—A synthetically prepared racemic mixture of bases having the formula  $C_6H_5CH_2CHNH_2CH_3$



**Actions and Uses.**—Amphetamine produces local effects similar to those of ephedrine. Inhalation of the vapors of amphetamine or its carbonate produces shrinking of the nasal mucosa in head colds, sinusitis, vasomotor rhinitis, hay fever and asthma. Both amphetamine and its carbonate (the latter readily forms on exposure of amphetamine to air) are volatile. Its use is contraindicated in those who suffer from cardiovascular disease and in those who show either sensitivity or pressor effect from its use in therapeutic doses.

**Dosage.**—As an inhalant, one or two inhalations through each nostril at hourly intervals, has been recommended. Continued overdosage should be guarded against, as this has caused restlessness and sleeplessness; and serious reaction has been reported as a result of overdosage and what may be hypersensitivity to the drug in inhalator form.

#### *Tests and Standards.*

Amphetamine occurs as a colorless, mobile liquid, boiling at 200–203 C., with slight decomposition. The specific gravity at 25 C is 0.931. The vapor pressure at ordinary temperature is relatively high, and the substance possesses a strong basic odor and a burning taste. It is soluble in ether a

Place 1 Gm. of amphetamine water and 5 cc. of 40 per cent benzoyl chloride, 0.5 cc. at a time, add the benzoyl chloride until the mixture becomes turbid. Recrystallize twice from ether; the melting point is 115–116 C. Recrystallize from benzoyl derivative by the method of H. J. Harwood, J. Pharm. Med., 1911, 2, 105. The melting point is more than 5.95 per cent.

Transfer 0.5 Gm. of amphetamine, accurately weighed, to a tared weighing bottle and place on the steam bath for one hour. The residue is not more than 0.5 per cent (nonvolatile compounds). Dissolve 1 cc. of benzedrine in 10 cc. of liquid petrolatum U. S. P. X. (anhydrous) and no turbidity is produced (water).

Substance, accurately weighed, in 10 cc. of water, acid, using methyl red as indicator, not less than 95 per cent, cc. half-normal sulfuric acid.

Determine carbon, hydrogen and nitrogen by micro combustion methods. The carbon should be not less than 79.7 nor more than 80.2 per cent, the hydrogen, not less than 9.6 nor more than 9.9 per cent, and the nitrogen, not less than 10.2 nor more than 10.6 per cent.

**AMPHETAMINE SOLUTION** Transfer an accurately weighed sample of benzedrine solution weighing about 15 Gm to a Kjeldahl distillation flask add 5 Gm. of iodine, distil 150 cc. into excess acid with tenth equivalent to not less

Transfer the foregoing solution to a separatory funnel and proceed to determine the melting point of benzoyl derivative as outlined under "Benzedrine Inhaler"

### SMITH, KLINE & FRENCH LABORATORIES

**Benzedrine Inhaler** Each inhaler tube contains at the time of packing, amphetamine 0.25 Gm, oil of lavender 0.075 Gm, and menthol 0.012 Gm

U S patents 1 921 424 (Aug 8 1933 expires 1950) 1 879 003 (Sept 27, 1932 expires 1949) and 2 015 403 (Sept. 24 1935 expires 1952)  
U S trademark 272 377

**BENZEDRINE INHALER** Transfer the filling to a Kjeldahl distillation flask add 250 cc of water and 1 Gm of sodium hydroxide, distil 150 cc into 20 cc of tenth normal sulfuric acid titrate the excess acid with tenth normal sodium hydroxide solution the base is equivalent to not less

Transfer the foregoing solution to a separatory funnel, extract with 10 cc of ether, shake the flask and contents for ten minutes set aside, at the end of two hours add 0.5 cc of benzoyl chloride shake the flask for ten minutes allow to stand on the steam bath until the odor of benzoyl chloride has disappeared, remove the precipitate by filtration wash with cold water dry at 90 C the melting point is 130-135 C

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**Actions and Uses**—Amphetamine sulfate is useful in the treatment of narcolepsy, for controlling symptoms similar to those of narcolepsy in the treatment of postencephalitic parkinsonism in the treatment of certain depressive conditions and as an adjunct in the treatment of alcoholism as indicated below and for facilitating roentgenographic studies of the gastrointestinal tract

Its use is not recommended in the treatment of sleepiness and fatigue in normal individuals because of the possible danger ofpressor effects from continued use, because of the dangers of eliminating the warning signal of sleepiness in individuals who are overdoing because of the possibility of fatal formation or addiction from such use and because cases of collapse have ensued when the drug has been used for this purpose. Its use is not recommended for developing a sense of increased energy or capacity for work or a feeling of exhilaration or as a "pick me up" in individuals other than those under the strict supervision of the physician. These effects of the drug may be useful in the symptomatic treatment of mild depressive states and, to a lesser extent, of severe depressions accompanying cer

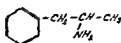


## CHAPTER VI

### AUTONOMIC DRUGS

#### Sympathomimetic Agents

**AMPHETAMINE.**—Racemic Amphetamine.—Alpha-methylphenethylamine.—1-phenyl-2-aminopropane.—Benzedrine.—Racemic desoxynor-ephedrine.—A synthetically prepared racemic mixture of bases having the formula  $C_6H_5CH_2CHNH_2CH_3$ .



**Actions and Uses**—Amphetamine produces local effects similar to those of ephedrine. Inhalation of the vapors of amphetamine or its carbonate produces shrinking of the nasal mucosa in head colds, sinusitis, vasomotor rhinitis, hay fever and asthma. Both amphetamine and its carbonate (the latter readily forms on exposure of amphetamine to air) are volatile. Its use is contraindicated in those who suffer from cardiovascular disease and in those who show either sensitivity or pressor effect from its use in therapeutic doses.

ness and sleeplessness; and serious reaction has been reported as a result of overdosage and what may be hypersensitivity to the drug in inhalator form.

#### *Tests and Standards.*—

Amphetamine occurs as a colorless, mobile liquid, boiling at 200–203 C., with slight decomposition. The specific gravity at 25 C. is 0.931. The vapor pressure at ordinary temperature is relatively high, and the substance possesses a strong basic odor and a burning taste. It is soluble in ether.

Place 1 Gm. of amphetamine in water and 5 cc. of 40 per cent benzoyl chloride, 0.5 cc. at a time, add the benzoyl chloride until the mixture becomes turbid. Recrystallize twice from ether; the melting point is 100–101 C. Recrystallize from ether; the melting point is 100–101 C. Recrystallize from ether; the melting point is 100–101 C. Recrystallize from ether; the melting point is 100–101 C.

Transfer 0.5 Gm. of amphetamine, accurately weighed, to a tared weighing bottle and place on the steam bath for one hour. The residue is not more than 0.5 per cent (nonvolatile compounds). Dissolve 1 cc. of benzedrine in 10 cc. of liquid petrolatum U. S. P. X. (anhydrous). No turbidity is produced (water).

Suspend about 1 Gm. of amphetamine, accurately weighed, in 10 cc. of water and titrate with half normal sulfuric acid, using methyl red as an indicator. The acid used corresponds to not less than 95 per cent nor more than 100 per cent of the base (1 cc. half normal sulfuric acid is equivalent to 0.0675 Gm. of base).

Determine carbon, hydrogen and nitrogen by micro combustion methods. The carbon should be not less than 79.7 nor more than 80.2 per cent, the hydrogen, not less than 9.6 nor more than 9.9 per cent, and the nitrogen, not less than 10.2 nor more than 10.6 per cent.

**AMPHETAMINE SOLUTION** Transfer an accurately weighed sample of benzedrine solution weighing about 15 Gm. to a Kjeldahl distillation flask add 5 Gm. of talc, 250 cc of water and 1 Gm. of sodium hydroxide, distil 150 cc. into 20 cc of tenth normal sulfuric acid, titrate the excess acid with tenth normal sodium hydroxide solution the base is equivalent to not less than 0.95 per cent nor more than 1.05 per cent.

Transfer the foregoing solution to a separatory funnel and proceed to determine the melting point of benzoyl derivative as outlined under "Benzedrine Inhaler."

### SMITH, KLINE & FRENCH LABORATORIES

**Benzedrine Inhaler** Each inhaler tube contains at the time of packing, amphetamine 0.25 Gm., oil of lavender 0.075 Gm., and menthol 0.012 Gm.

U S patents 1 921 424 (Aug. 8, 1933, expires 1950) 1 879 003 (Sept. 27, 1932, expires 1949) and 2 015 408 (Sept. 24, 1935, expires 1952)  
U S trademark 272, 377

**BENZEDRINE INHALER** Transfer the filling to a Kjeldahl distillation flask, add 250 cc of water and 1 Gm. of sodium hydroxide, distil 150 cc into 20 cc of tenth normal sulfuric acid, titrate the excess acid with tenth normal sodium hydroxide solution the base is equivalent to not less than 0.305 Gm. nor more than 0.360 Gm. per tube.

Transfer the solution from the titration to a separatory funnel, extract with 30 cc. of ether, transfer the aqueous layer to an Erlenmeyer flask add 2 cc. of 40 per cent sodium hydroxide solution and 0.5 cc. of benzoyl chloride and shake the flask and contents for ten minutes set aside for two hours, add 0.5 cc. of benzoyl chloride, shake the flask and contents for ten minutes set aside, at the end of two hours add 0.5 cc. of benzoyl chloride, shake the flask for ten minutes allow to stand on the steam bath until the odor of benzoyl chloride has disappeared, remove the precipitate by filtration, wash with cold water dry at 90 C., the melting point is 130-135 C.

**AMPHETAMINE SULFATE.**—Racemic Amphetamine Sulfate.—Alpha methylphenethylamine sulfate—Benzedrine Sulfate—Racemic desoxynor-ephedrine sulfate—1 phenyl-2-amino propane sulfate— $[C_6H_5CH_2CH(NH_2)CH_3]_2H_2SO_4$ .

**Actions and Uses**—Amphetamine sulfate is useful in the treatment of narcolepsy, for controlling symptoms similar to those of narcolepsy in the treatment of postencephalitic parkinsonism in the treatment of certain depressive conditions and as an adjunct in the treatment of alcoholism as indicated below and for facilitating roentgenographic studies of the gastrointestinal tract.

" . . . . . the treatment of sleepiness and  
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addiction from such use and because cases of collapse have  
ensued when the drug has been used for this purpose. Its use  
is not recommended for developing a sense of increased energy  
or capacity for work or a feeling of exhilaration or as a  
"pick me up" in individuals other than those under the strict  
supervision of the physician. These effects of the drug may be  
useful in the symptomatic treatment of mild depressive states  
and, to a lesser extent, of severe depressive acute jangling cer

tain major psychopathic conditions. Evidence indicates that the drug is of little value in altering the course of the underlying psychosis in the latter conditions and that results are not striking in the psychoneuroses. In severe depressive psychopathic cases, patients should be institutionalized, and in mild psychogenic disorders the use of the drug should be subordinated to efforts directed toward correction of the underlying causes. It is useful primarily in depression due to apathy and psychomotor retardation in patients manifesting anxiety and restlessness. There is also evidence of its influence on mental depression racemic amphetamine sulfate may be useful as an adjunct to permit institution of the usual and more fundamental psychotherapeutic measures in the treatment of alcoholic addiction (chronic alcoholism) when the depression is due solely to the alcohol. The drug appears to be more effective in acute alcoholism with or without accompanying psychosis—to combat pathologic intoxication. In alcoholic psychoses best results are reported in cases where the psychosis is of recent origin. More experience with the drug is needed before its benefits and its dangers can be fully evaluated; however, the possibility that deleterious effects may be produced from habituation to the drug must be constantly kept in mind. Its indiscriminate administration to patients with psychic disorders and its use for simple "hangover" following temporary alcoholic overindulgence are to be condemned. It is reported that the pressor effect of the drug has some value in the symptomatic treatment of orthostatic hypotension. It has been used in the treatment of spastic colitis and pyloric spasm and in many other clinical conditions not mentioned above, but its use for these purposes is not recommended at present.

The very nature of the therapeutic effects, as well as the side actions of this drug, requires that its use be promoted with proper caution as to pressor effect, hyperexcitability, gastrointestinal disturbance, restlessness, sleeplessness and in overdose, chills, collapse and syncope. There is evidence that the barbiturates are useful to control overdose. It should also be carefully noted that the drug is contraindicated in cardiovascular disease, especially when hypertension is a sequence of that disease.

Amphetamine sulfate have been exploited for weight reduction. The Council has examined them and found them wanting. The Council has disapproved of the use of amphetamine sulfate in the treatment of obesity.

**Dosage.**—Initial doses should be small, ranging from 2.5 to 10 mg., and increased gradually until a definite effect manifests itself. The use of small test doses is particularly important

in the treatment of depressive states. Effective dosage varies considerably depending on the condition being treated. In certain cases it may be necessary to repeat the use of the drug three times daily, but it is recommended that such a dosage not exceed 10 to 20 mg. It is preferable if possible, to administer the effective quantity of this drug during the morning to avoid interference with sleep.

#### Tests and Standards—

Amphetamine sulfate occurs as a white odorless powder, freely soluble in water, slightly soluble in alcohol, insoluble in ether. Its aqueous solution is neutral to litmus. Amphetamine sulfate melts at over 300 C.

content of the benzoyl derivative by the micro Dumas method is not less than 5.70 per cent nor more than 5.95 per cent.

Dry about 0.5 Gm. of amphetamine sulfate, accurately weighed, to constant weight at 100 C.; the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. of amphetamine sulfate accurately weighed; the residue is not more than 0.1 per cent.

Transfer 0.3 Gm. of amphetamine sulfate accurately weighed to a

content is not less than 72 per cent nor more than 73.5 per cent.

#### SMITH KLINE & FRENCH LABORATORIES

**Ampules Benzedrine Sulfate Solution.** 10 mg. of amphetamine sulfate in 1 cc. of sterile water made isotonic with sodium chloride.

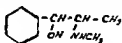
**Benzedrine Sulfate Tablets.** Amphetamine sulfate 5 mg. and 10 mg.

U. S. patent 1,879,003 (Sept. 27, 1932, expires 1949); 1,921,424 (Aug. 8, 1933, expires 1950) and 2,015,405 (Sept. 24, 1935, expires 1952).  
U. S. trademark 272,377.

**EPHEDRINE**—An alkaloid obtained from *Ephedra equisetina* Bunge, *Ephedra sinica* Stapf and other species of *Ephedra* (fam. *Gnetales*) or produced synthetically. It is anhydrous or contains not more than one-half molecule of water of hydration. Anhydrous Ephedrine contains not less than 98.5 per cent of  $C_{10}H_{15}NO$ . Hydrated Ephedrine contains not less than 94 per cent of  $C_{10}H_{15}NO$ . U. S. P.

For description and standards see the U. S. Pharmacopeia under Ephedrina.

Ephedrine is an alkaloid first obtained by Nagai in 1887 from a Chinese herb, ma huang (*Ephedra equisetina*). Chemically, ephedrine is 1-phenyl-2-methylamine-propanol-1, ( $C_6H_5CHOHCH(NHCH_3).CH_3$ ). Structurally, it is closely related to epinephrine, and like epinephrine it is levorotatory; but it is more stable. Its salts are, in general, soluble in water and in alcohol.



**Actions and Uses.**—Ephedrine produces effects somewhat similar to those of epinephrine. However, it is difficult to explain its actions without postulating a direct stimulation of smooth muscle as well as a stimulating effect on the sympathetic nervous system. In small doses ephedrine has a stimulating action on the heart, increasing the rate and the strength of contractions and raising the blood pressure. In large and toxic doses the drug has a depressant action on the heart muscle. It causes a rather lasting rise of blood pressure, on intravenous or intramuscular injection, due mainly to vasoconstriction. Other effects similar to those of epinephrine are dilatation of the bronchi and mydriasis after local or systematic administration. On local application to mucous membranes or wounds it contracts the capillaries to a moderate degree and thus diminishes hyperemia and reduces swelling. Ephedrine is used locally in the eye to dilate the pupils, and in the nostrils to shrink the congested mucosa in rhinitis and sinusitis. The systemic effects can be obtained by oral as well as by hypodermic or intramuscular administration. Ephedrine is useful against asthma, especially to prevent the attacks; but it often fails partially or completely. It is also used against hay fever and urticaria. It tends to produce symptoms of the anxiety complex. This may constitute a definite contraindication to its use. Its use in serious heart disease is not yet considered safe. Ephedrine is used to sustain the blood pressure in spinal anesthesia, but it is still questionable whether the drug is of real benefit in shock, hypotension and circulatory collapse and hemorrhage. It is of value in preventing the muscle weakness of myasthenia gravis. It is without value in Addison's disease.

**Dosage.**—Salts of ephedrine are quite effective whether given orally, intramuscularly, intravenously, or by any ordinary path of administration. For local application to mucous membranes it is used in 0.5 to 2 per cent solution of a salt of ephedrine; in ophthalmologic work it has been used in 4 per cent solution. Orally, the usual dose for adults is from 20 to 50 mg. every 3 to 4 hours.

## ABBOTT LABORATORIES

Ephedrine (Powder) bulk

## GANE AND INGRAM, INC

Ephedrine (Powder) bulk

## MERCK &amp; Co INC

Ephedrine (Powder) bulk

**EPHEDRINE HYDROCHLORIDE** — When dried over sulfuric acid for 18 hours contains not less than 80 per cent and not more than 82.5 per cent of anhydrous ephedrine ( $C_{10}H_{15}NO$ ) U S P

For description and standards see the U S Pharmacopeia under Ephedrinae Hydrochloridum and the National Formulary under Tabellae Ephedrinae Hydrochloridi

*Actions and Uses* — See preceding article Ephedrine

*Dosage* — See preceding article Ephedrine

## ARROTT LABORATORIES

Ampuls Solution Ephedrine Hydrochloride 5 per Cent  
1 cc

Capsules Ephedrine Hydrochloride 24 mg 37.4 mg  
and 49 mg

Solution Ephedrine Hydrochloride 3 per Cent Preserved with chlorobutanol 0.5 per cent

Syrup Ephedrine Hydrochloride Contains ephedrine hydrochloride 0.2195 Gm in 100 cc and alcohol 12 per cent

Syrup Ephedrine Hydrochloride (Double Strength) Containing ephedrine hydrochloride 0.4390 Gm in 100 cc and alcohol 12 per cent

Tablets Ephedrine Hydrochloride 32.5 mg

## AMERICAN PHARMACEUTICAL Co INC

Solution Ephedrine Hydrochloride, 3 per Cent 1 fluid ounce bottle Preserved with 0.5 per cent chlorobutanol

Capsules Ephedrine Hydrochloride 25 mg and 50 mg

## GEORGE A BREON &amp; COMPANY INC

Caplets Ephedrine Hydrochloride 50 mg

Solution Ephedrine Hydrochloride 3%, 29.5 cc and 480 cc bottles 0.5 per cent chlorobutanol added as preservative

## BURNOUGH'S WELLCOME &amp; Co INC

Ephedrine Hydrochloride (Powder) 15 cc and 30 cc bottles

Hypoloid Ephedrine Hydrochloride Injection 30 mg in 1 cc.

**Solution Ephedrine Hydrochloride, 3 per cent:** Preserved with chlorobutanol 0.5 per cent; 1 fluidounce and 1 pint bottles.

**Tabloid Ephedrine Hydrochloride:** 0.016 Gm and 0.032 Gm.

**ENDO PRODUCTS, INC.**

**Capsules Ephedrine Hydrochloride:** 24 mg., 324 mg. and 49 mg

**GANE AND INGRAM, INC.**

**Ephedrine Hydrochloride (Powder):** bulk.

**THE LAKESIDE LABORATORIES, INC.**

**Solution Ephedrine Hydrochloride, 3 per Cent:** Preserved with chlorobutanol, 0.5 per cent.

**ELI LILLY AND COMPANY**

**Pulvules Ephedrine Hydrochloride:** 25 mg. and 50 mg

**Solution Ephedrine Hydrochloride, 3 per Cent:** Preserved with chlorobutanol, 0.5 per cent.

**Syrup Ephedrine Hydrochloride:** Contains ephedrine hydrochloride, 0.22 Gm., in 100 cc. and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth

**MERCK & Co., INC.**

**Ephedrine Hydrochloride (Powder):** bulk.

**PARKE, DAVIS & COMPANY**

**Capsules Ephedrine Hydrochloride:** 25 mg. and 50 mg.

**PITMAN-MOORE COMPANY**

**Capsules Ephedrine Hydrochloride:** 24 mg

**SHARP & DOHME, INC.**

**Capsules Ephedrine Hydrochloride:** 25 mg.

**THE WARREN-TEED PRODUCTS Co.**

**Capsules Ephedrine Hydrochloride:** 25 mg and 50 mg

**EPHEDRINE SULFATE.**—"When dried over sulfuric acid for 18 hours, contains not less than 75.5 per cent and not more than 77.3 per cent of anhydrous ephedrine ( $C_{10}H_{15}NO$ )."  
U. S. P

For description and standards see the U S Pharmacopeia under Ephedrinae Sulfas and Tabellae Ephedrinae Sulfatis and

the National Formulary under *Ampullae Ephedrinae Sulfatis*, *Gelatum Ephedrinae Sulfatis*, *Liquor Ephedrinae Sulfatis* and *Syrupus Ephedrinae Sulfatis*

*Actions and Uses*—See preceding article *Ephedrine*

*Dosage*—See preceding article *Ephedrine*

#### ABBOTT LABORATORIES

**Ampuls Solution Ephedrine Sulfate** 25 mg in 1 cc and 50 mg in 1 cc

**Capsules Ephedrine Sulfate** 24 mg and 50 mg

**Solution Ephedrine Sulfate 3 per Cent** Preserved with chlorobutanol 0.5 per cent

#### AMERICAN PHARMACEUTICAL CO. INC.

**Solution Ephedrine Sulfate, 3 per Cent** 1 fl. ounce bottle Preserved with 0.5 per cent chlorobutanol

**Capsules Ephedrine Sulfate** 25 mg and 50 mg

#### GEORGE A. BREON & COMPANY, INC.

**Ephedrine Sulfate 1%, Nasal Jelly with Sodium Chloride** 15 Gm collapsible tube **Ephedrine sulfate 1 per cent with sodium chloride 0.8 per cent** in a water soluble boroglycerin jelly base

#### BURROUGHS WELLCOME & CO. INC.

**Ephedrine Sulfate (Powder)** 15 cc and 30 cc bottles

**Hypoid Ephedrine Sulfate Injection** 0.049 Gm in 1 cc

**Solution Ephedrine Sulfate 3 per Cent** Preserved with chlorobutanol 0.5 per cent 1 fl. ounce and 1 pint bottles

#### LANO PRODUCTS, INC.

**Ampul Solution Ephedrine Sulfate** 0.05 Gm in 1 cc

**Tablets Ephedrine Sulfate** 24 mg

**Solution Ephedrine Sulfate 3 per Cent** 29.5 cc bottle Preserved with 0.5 per cent chlorobutanol

#### GANE AND INGHAM, INC.

**Ephedrine Sulfate (Powder)** 1 lb.

#### THE FALISCH LABORATORIES, INC.

**Ampuls Solution Ephedrine Sulfate** 50 mg in 1 cc

**Capsules Ephedrine Sulfate** 25 mg and 50 mg

#### FELLMAN AND COMPANY

**Ampuls Solution Ephedrine Sulfate** 25 mg in 1 cc and 50 mg in 1 cc



**Elixir Ephedrine Sulfate:** Contains ephedrine sulfate, 0.44 Gm. in 100 cc. in a menstruum composed of alcohol 12 per cent, glycerin, sucrose and water, flavored with gluside, oenanthic ether, oil of orange, oil of coriander, oil of caraway, oil of lemon, oil of cassia, oil of anise, saffrol and vanillin.

**Ephedrine Jelly:** Ephedrine sulfate, 1 Gm.; glycerin, 15 Gm.; tragacanth, 1 Gm.; eucalyptol, 0.1 Gm.; oil of wintergreen, 0.01 Gm.; oil of dwarf pine needles, 0.01 Gm.; sodium phosphate U. S. P., 0.16 Gm.; water to make 100 Gm.

**Pulvules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Solution Ephedrine Sulfate 3 per Cent:** Preserved with chlorobutanol, 0.5 per cent.

**Syrup Ephedrine Sulfate:** Containing ephedrine sulfate, 0.22 Gm., in 100 cc. and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amarantli.

**Syrup Ephedrine Sulfate (Double Strength):** Containing ephedrine sulfate, 0.44 Gm., in 100 cc. and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

#### THE MALTBE CHEMICAL COMPANY

**Ephedrine Nasal Jelly:** Ephedrine sulfate, 1 per cent, and sodium benzoate 0.5 per cent in a glycerite of tragacanth base

#### MERCK & Co., INC.

**Ephedrine Sulfate (Powder):** bulk.

#### PARKE, DAVIS & COMPANY

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Glaseptic Ampoules Solution Ephedrine Sulfate:** 50 mg. in 1 cc.

**Solution Ephedrine Sulfate, 3 per Cent:** Preserved with chlorobutanol 0.5 per cent

#### SHARP & DOHME, INC.

**Ampuls Solution Ephedrine Sulfate:** 48 mg. in 1 cc. Preserved with 0.5 per cent of chlorobutanol.

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Solution Ephedrine Sulfate 3 per Cent:** Preserved with chlorobutanol, 0.5 per cent.

#### THE SMITH-DORSEY COMPANY

**Capsules Ephedrine Sulfate:** 25 mg and 50 mg.

#### THE UPJOHN COMPANY

**Ampules Solution Ephedrine Sulfate:** 50 mg. in 1 cc.

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.



lization from ether and drying at room temperature over phosphorus pentoxide in a slight vacuum, the racephedrine melts at 76 C.

Dissolve approximately 0.2 Gm. of racephadrine in 8 cc. of distilled water; add 1 drop of 2 per cent copper sulfate solution and 1 cc. of 20 per cent sodium hydroxide solution; a purple color is developed which, on shaking with ether, is partially dissolved in the ether layer; evaporate the ether layer; a pinkish residue remains. Place a drop of a 5 per cent solution of racephadrine hydrochloride on a microscopic slide and introduce a small solid particle of potassium oxalate at an edge of the drop; a crystalline precipitate immediately appears. The form of the crystals allows the making of distinction between optically active and racemic forms of ephedrine hydrochloride. The former gives bundles of needles and prisms; the latter, thin plates.

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**GANE'S CHEMICAL WORKS, INC.**

**Racephedrine Hydrochloride (Crystals):** bulk.

THE UPJOHN COMPANY

**Capsules Racephedrine Hydrochloride: 25 mg.**

**Racephedrine Hydrochloride 1 per Cent in Ringer's Solution:** Contains in each 100 cc. racephedrine hydrochloride-N. N. R., 1 Gm, chlorobutanol, 0.5 Gm, sodium chloride, 0.86 Gm, potassium chloride, 0.03 Gm., and calcium chloride, 0.033 Gm dissolved in distilled water.

**RACÉPHEDRINE SULFATE.**—Racemic Ephedrine Sulfate.— $C_{10}H_{15}ON.H_2SO_4$

*Actions and Uses*—The same as those of l-ephedrine sulfate

*Dosage.*—From 30 to 50 mg.

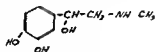
### Tests and Standards—

Racephedrine sulfate is a colorless, crystalline substance. The melting point is 247 C (microscopic heating stage). The solubility is fair in water and alcohol. Dissolve 0.5 Gm. in 25 cc of distilled water. The aqueous solution is neutral to litmus and does not show optical activity. The U S P XI test for chloride is also negative. Weigh out accurately 0.25 Gm of racephedrine sulfate and dry to constant weight over sulfuric acid in a desiccator at room temperature; the loss is not more than 2 per cent of its weight, 0.23 Gm of racephedrine sulfate has a negligible ash residue. The assay for anhydrous racephedrine, as described in racephedrine hydrochloride, is not more than 77.5 per cent nor less than 75.5 per cent.

**GANE'S CHEMICAL WORKS, INC.**

**Racephedrine Sulfate (Crystals):** bulk

**EPINEPHRINE—U S P** Epinephrine the active principle of the medullary portion of the suprarenal glands is extensively used in surgery and to a less extent in medicine in the form of the 1 in 1000 solution of epinephrine hydrochloride (solution of epinephrine hydrochloride, U S P) The alkaloid in addition to being obtained from the suprarenal glands is also prepared synthetically and such preparations if they are levorotatory are equally as active as the natural product Artificial epinephrines have also been prepared which are optically inactive and as such are only about half as active physiologically as is natural epinephrine Dextrorotatory epinephrine is almost inactive



For description and standards see the U S Pharmacopeia under *Epinephrina Injectio Epinephrinae Hydrochloridi* and *Nebula Epinephrinae Hydrochloridi*

**Actions and Uses**—Epinephrine acts peripherally on a variety of structures by stimulating the myoneural junctions of the sympathetic nerve endings. Its most important actions consist of a constriction of the blood vessels of the skin dilatation of blood vessels of the voluntary muscles stimulation of the heart with an increase in cardiac output a rise in systolic arterial pressure and a widening of pulse pressure Relaxation of the bronchial muscles and also glycosuria follow intramuscular or hypodermic injection Moderate doses when given by mouth have practically no action However in hypersensitive patients such as those with thyrotoxicosis the administration of epinephrine by mouth may occasionally produce typical effects The effect of a single intravenous dose is fleeting

Epinephrine is used locally for its vasoconstrictor action in hemorrhage and in catarrhal and congestive conditions It often relieves asthmatic paroxysms when used by hypodermic injection because of the marked increase in vital capacity produced by the drug it is most valuable for treating a severe acute attack of asthma If however asthmatic paroxysms are frequent it is generally advisable to use ephedrine with or in place of epinephrine Intravenous injections are sometimes effective in shock and anesthesia accidents (care being taken not to give an overdose) It is of little or no value in Addison's disease Epinephrine in the form of a 2 per cent solution of a salt of epinephrine has been used locally in the treatment of glaucoma with apparently favorable results in certain cases while in other cases it appears to be ineffective

Epinephrine is contraindicated in cyclopropane or chloroform anesthesia because of its potential danger as a cardiac stimulant in connection with these drugs

The vasoconstrictor action of epinephrine is used to prolong

In the same manner it is believed to lessen the toxicity of the local anesthetics by retarding their absorption into the general circulation.

Dilute watery solutions rapidly lose their strength, the deterioration being accompanied by a reddish or brownish discoloration.

To guard against too great a local ischemia, which may lead to local death of tissue, the concentration of epinephrine in the local anesthetic solution should not be greater than 1:50,000.

To guard against a possible systemic reaction due to absorption of epinephrine, the total dose of this drug injected with a local anesthetic solution at one time should never be greater than 1 mg. (1 cc.).

**Dosage.**—*Hypodermically or intramuscularly* from 0.06 to 1 cc. of a 1 in 1,000 solution of epinephrine hydrochloride. *Locally*, it is used in solution varying in strength from 1 in 15,000 to 1 in 1,000. Epinephrine is also used in solution, in ointment for application to mucous membranes, such as the eye or the nose, where a slower but more lasting action is desired, and in suppositories.

#### THE ARMOUR LABORATORIES

**Suprarenalin (Crystals):** 63 mg. vials. Epinephrine

U. S. patent 829,220 (Aug. 21, 1906; expired).

**Ampules Suprarenalin Solution 1:10,000 (for Hypodermic Use):** 1 cc. Contains suprarenalin (epinephrine) as hydrochloride 0.01 per cent; chlorobutanol (chloroform derivative) 0.50 per cent, sodium bisulfite (not more than) 0.10 per cent; physiological salt solution Q S

#### PARKE, DAVIS & COMPANY

**Adrenalin (Crystals):** bulk.

U. S. patents 730,175, 730,176, 730,196, 730,197, 730,198 (June 2 1903, expired), 753,177 (Feb. 23, 1904, expired). U. S. trademark 53,934.

**Adrenalin Inhalant with Chloretone 3 per Cent:** A glycerin solution containing 1 part of adrenalin (as adrenalin chloride) in 1,000, 3 per cent of chloretone, 15 per cent of alcohol, and aromatics.

**Adrenalin Ointment:** Contains adrenalin chloride equivalent to one part of adrenalin in 1,000 parts of oleaginous ointment base.

**Adrenalin Suppositories:** One part of adrenalin (as adrenalin chloride) to 1,000 parts of oil of theobroma (cacao butter) and not more than 0.2 per cent of sodium bisulfite. Each suppository weighs about 1 Gm.

**Adrenalin Tablets** 1 mg Adrenalin as borate yielding a 1 in 1000 solution when dissolved in 1 cc of water Each tablet contains not more than 1 mg of sodium bisulfite

**Adrenalin Tablets** 0.33 mg Each contains adrenalin 0.33 mg as borate yielding a 1 in 1000 solution when dissolved in water Each tablet contains not more than 0.33 mg of sodium bisulfite

**Adrenalin and Cocaine Tablets** Each hypodermic tablet contains cocaine hydrochloride 0.01 Gm adrenalin 0.05 mg and not more than 0.33 mg of sodium bisulfite

**Ampoule Adrenalin Chloride Solution** 1:10,000 1 cc a sterile solution containing 1 part of epinephrine hydrochloride in 10,000 parts of physiological solution of sodium chloride with not more than 0.1 per cent of sodium bisulfite as a preservative

**Ampoule Adrenalin Chloride Solution** 1:2,600 1 cc a sterile solution containing 1 part of epinephrine hydrochloride in 2,600 parts of physiological solution of sodium chloride with not more than 0.1 per cent of sodium bisulfite as a preservative

#### THE UPJOHN COMPANY

**Epinephrine (Crystals)** 65 mg vials

**Ampules Solution Epinephrine** 1:1,000 1 cc Each cubic

Saturated with calcium chloride

**Solution Epinephrine** 1:1,000 30 cc vials Each cubic

Saturated with calcium chloride

#### THE WILSON LABORATORIES

**Epinephrine (Crystals)** bulk

#### WINTHROP CHEMICAL COMPANY, INC.

**Suprarenin**—Epinephrine made synthetically by the method of Stolz and Flaecher (Ztschr f physiol Chem, vol 58 p 189)

**Ampules Suprarenin Bitartrate Powder** 0.05 Gm Each ampul contains suprarenin bitartrate 0.091 Gm equivalent to suprarenin 0.05 Gm

**Ampules Suprarenin Bitartrate Solution** 1:1,000 Each 1 cc contains suprarenin bitartrate equivalent to suprarenin 0.001 Gm

**Suprarenin Bitartrate Solution** 1:1,000 Each 1 cc. contains suprarenin bitartrate equivalent to suprarenin 0.001 Gm and 0.5 per cent chlorobutanol

**Tablets Suprarenin Bitartrate:** 1 mg. Each tablet contains suprarenin bitartrate equivalent to 1 mg. of suprarenin.

**Tablets Suprarenin Bitartrate:** 20 mg. Each tablet contains suprarenin bitartrate 0.0364 Gm., equivalent to suprarenin 0.02 Gm., with lactose 0.0385 Gm., and acetone sodium bisulfite not more than 0.1 mg.

U. S. patent 986,136 (March 7, 1911; expired).

**SOLUTION OF EPINEPHRINE HYDROCHLORIDE.**—"A solution of epinephrine hydrochloride in distilled water having a potency equivalent to a solution containing 1 Gm. of U. S. P. Epinephrine Reference Standard in each 1,000 cc." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under *Liquor Epinephrinae Hydrochloridi*.

*Actions and Uses.*—See Epinephrine.

*Dosage.*—See Epinephrine.

#### ABBOTT LABORATORIES

**Ampoule Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. contains sodium bisulfite 0.2 per cent as a preservative.

**Solution Epinephrine Hydrochloride 1:1,000:** 30 cc. safety container for parenteral or topical use contains sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent as a preservative.

#### THE ARMOUR LABORATORIES

**Ampule Suprarenalin Solution 1:1,000:** 1 cc. contains epinephrine hydrochloride 0.1 per cent, chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent in isotonic solution of sodium chloride.

**Suprarenalin Solution 1:1,000:** 5 cc., 10 cc. and 30 cc. vials for hypodermic use. Contains epinephrine hydrochloride 0.1 per cent, chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent in isotonic solution of sodium chloride.

**Suprarenalin Solution 1:1,000:** 30 cc. bottle for topical use. Contains epinephrine hydrochloride 0.1 per cent, chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent in isotonic solution of sodium chloride.

#### GEORGE A. BREON & COMPANY, INC.

**Ampul Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. Contains chlorobutanol 0.5 per cent and sulfurous acid not more than 0.06 per cent in isotonic solution of sodium chloride.

#### CHEPLIN BIOLOGICAL LABORATORIES, INC.

**Ampules Epinephrine Hydrochloride Solution 1:1,000:** 1 cc. contains chlorobutanol 0.5 per cent and sodium bisulfite

0.1 per cent as preservatives in isotonic solution of sodium chloride

**Epinephrine Hydrochloride Solution** 1 1,000 10 cc and 30 cc vials for parenteral injection. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives in isotonic solution of sodium chloride

**Epinephrine Hydrochloride Solution** 1 1,000 30 cc bottle for topical administration. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives in isotonic solution of sodium chloride

#### ENDO PRODUCTS, INC.

**Ampul Solution Epinephrine Hydrochloride**, 1 1,000 1 cc. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative in isotonic solution of sodium chloride

**Solution Epinephrine Hydrochloride** 1 1,000 30 cc vials (rubber stoppered and cork stoppered). Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative in isotonic solution of sodium chloride

#### FIRST LAKESIDE LABORATORIES, INC.

**Ampul Solution of Epinephrine Hydrochloride**, 1 1,000 1 cc. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative in isotonic solution of sodium chloride saturated with carbon dioxide

**Solution of Epinephrine Hydrochloride** 1 1,000 30 cc vials. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative in isotonic solution of sodium chloride saturated with carbon dioxide

#### FIDELITY LABORATORIES, INC.

**Ampoule Sterile Solution Epinephrine Hydrochloride** 1 1,000 1 cc contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives

**Sterile Solution Epinephrine Hydrochloride** 1 1,000 5 cc and 30 cc vials for parenteral injection. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives

#### PARKE, DAVIS & COMPANY

**Ampoule Adrenalin Chloride Solution** 1 1,000 1 cc contains epinephrine hydrochloride 0.1 per cent in isotonic solution of sodium chloride with chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives

#### U. S. STANDARD PRODUCTS CO.

**Ampoule Epinephrine Hydrochloride Solution** 1 1,000 1 cc contains chlorobutanol 0.5 per cent as a preservative



**Epinephrine Hydrochloride Solution 1:1,000:** 30 cc. bottle, for topical use. Contains chlorobutanol 0.5 per cent as a preservative.

#### THE WILSON LABORATORIES

**Solution Epinephrine Hydrochloride 1:1,000:** 30 cc. bottles and vials, for topical use. Contains chlorobutanol 0.5 per cent and sulfuric acid not more than 0.06 per cent as preservatives in isotonic solution of sodium chloride.

#### SUSPENSION OF EPINEPHRINE IN OIL, 1:500.

—Suspension of epinephrine base 1:500. A 0.2 per cent suspension, containing 1 part of epinephrine U. S. P. to 500 parts of vegetable oil.

*Actions and Uses.*—Injections of solutions of epinephrine salts (1:1,000) are known to provide prompt but transient relief in the treatment of severe attacks of bronchial asthma by relaxation of the bronchial muscles. Recent evidence indicates that injections of vegetable oil suspensions of epinephrine base (1:500) delay but prolong the action of the drug and thus provide more sustained symptomatic relief in this condition as well as in certain cases of hay fever, urticaria, angioneurotic edema and serum sickness. The usual contraindications to epinephrine must be kept in mind. The preparation should not be given to the aged or to patients with hypertension, because of its prolonged pressor effects. Its sustained action may also prolong disagreeable side effects as well as serious reactions due to overdosage in less tolerant individuals. Local reactions due to irritation by the oil, especially when injected subcutaneously, have also been reported. For this reason it is recommended that it be administered intramuscularly and that particular attention be paid to the possibility of scar formation (fibrosis) at the sites of injection. Reactions from the epinephrine itself may be partially avoided by adequate resuspension (shaking) of any precipitate in the oil, the use of a dry syringe and needle, and precaution to prevent injecting directly into the blood stream by withdrawal of the syringe plunger to determine the location of the needle point in relation to a vessel before each injection and caution in the selection of the initial dose. The use of a small caliber needle to minimize trauma to blood vessels is also recommended. Intravenous injection is, of course, contraindicated.

*Dosage*—Intramuscularly from 0.2 cc. to 1.5 cc. (0.4 mg. to 30 mg. epinephrine base) administered every eight to sixteen hours. The initial dose for adults should never exceed 0.5 cc. (1 mg. epinephrine base) and caution is necessary when subsequent doses larger than 1.0 cc are employed because of the unusually large amount of active material introduced (1 cc. of the oil suspension 1:500 is the equivalent of 2 cc. of an epinephrine solution 1:1,000) and its more prolonged action. Doses in excess of 1.5 cc are not recommended.

*Tests and Standards—*

Epinephrine in oil occurs as a pale yellow to white milky suspension from which a white solid settles out on standing. Centrifugate an ampule of epinephrine in oil until the crystals have collected in the bottom, open the ampule, decant the clear oil, and wash the residue with two 1 cc. portions of acetone by decantation. The residue, dried at 75 C., melts above 215 C., when heated at a rate of 8 degrees per minute.

Transfer an accurately measured volume of epinephrine in oil, containing approximately 8 mg. of epinephrine to a centrifuge tube. Centrifuge, wash and dry as described above. Dissolve the residue in 0.40 cc. of normal hydrochloric acid, filter and polarize in a micro-polariscope tube. The specific rotation  $[\alpha]_{\frac{25}{D}}$  is between  $-50.0$  and  $-53.5$  degrees.

Shake 10 cc. of epinephrine in oil with 50 cc. of tenth normal hydrochloric acid, add 20.0 cc. of distilled water, shake, filter through a paper previously moistened with water. Discard the first 5 cc. and save the remainder for the test. To 20.0 cc. of 0.5 per cent potassium permanganate solution add 10 cc. of 10% sodium hydroxide solution, 38 C., cool to room temperature, and compare in a colorimeter. The epinephrine content is not more than 2.15 nor less than 1.85 mg. per cc.

**ENDO PRODUCTS, INC.**

**Ampoule Epinephrine in Oil, 1:500; 1 cc.** A suspension of 2 milligrams of epinephrine in 1 cc. of peanut oil.

**THE LAKESIDE LABORATORIES, INC.**

**Ampules Epinephrine in Oil, 1:500; 1 cc.** A suspension of 2 mg. powdered epinephrine crystals in 1 cc. of sesame oil.

**PARKE, DAVIS & COMPANY**

**Ampoule Adrenalin in Oil 1:500; 1 cc.** A suspension of 2 mg. of crystalline epinephrine in 1 cc. of peanut oil.

**THE SMITH-KORTH COMPANY**

**Ampul Epinephrine in Oil, 1:500; 1 cc.** A suspension of 2 milligrams of crystalline epinephrine in 1 cc. of peanut oil.

**L. R. SQUIBB & SONS**

**Ampule Epinephrine in Oil 1:500; 1 cc.** A suspension of 2 mg. of crystalline epinephrine in 1 cc. of peanut oil.

**SOLUTION OF EPINEPHRINE HYDROCHLORIDE 1:100.**—A solution containing 1 part of epinephrine hydrochloride U. S. P. in 100 parts of isotonic solution of sodium chloride.

**Actions and Uses.**—Injections of a solution of epinephrine (1:1000) are known to be useful in the treatment of severe attacks of bronchial asthma. Recent evidence indicates that the oral inhalation of a solution of epinephrine ten times as strong as those used by hyperstemic subjects gives relief in acute

attacks of bronchial asthma when other measures fail. The physician should familiarize himself with the procedure before employing it in the treatment of his patients. It is absolutely essential that such treatment be instituted under the supervision of the physician and the patient warned of the dangers of using a solution of such strength carelessly. It is also necessary that the atomizer or nebulizer which is used in the administration of such solutions produce a fine mistlike spray free from minute droplets. Every precaution must be taken to avoid confusion between this solution (1:100) and the official 1:1,000 solution of epinephrine hydrochloride, since the 1:100 solution is not suitable for hypodermic use and should never be employed in that manner.

**Dosage**—A definite dosage cannot be stated for the use of this preparation. It is obviously essential that the amounts used not exceed the minimal amount which will give effective relief. It is best to start with a single compression of the bulb of the atomizer or nebulizer until it is determined what dosage is adequate and safe. Its use should not be repeated until several minutes have passed so that the full effect of the inhalation can be observed before additional amounts are used.

#### **THE ALEXON LABORATORIES**

**Suprarenalin Solution 1:100:** A solution of epinephrine hydrochloride 1.0 per cent, containing chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives.

#### **THE LAKESIDE LABORATORIES, INC.**

**Solution of Epinephrine Hydrochloride, 1:100:** 5 cc. screw-capped vials. Each cubic centimeter contains epinephrine hydrochloride, 0.5 per cent chlorobutanol and 1 per cent sodium bisulfite in isotonic sodium chloride solution saturated with carbon dioxide.

#### **LEDERLE LABORATORIES, INC.**

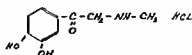
**Strong Solution of Epinephrine Hydrochloride 1:100:** 5 cc. vial. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium bisulfite.

#### **PARKE, DAVIS & COMPANY**

**Solution of Adrenalin Chloride 1:100:** 5 cc. vial. A solution of epinephrine hydrochloride 1.0 per cent, containing chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives.

**KEPHRI**  
acetocatechol  
methyraminoet  
(CH<sub>3</sub>) HCl.

of a base resembling epinephrine (*laevo*-methylaminoethanol catechol) but differs in that kephrine possesses a ketone group in place of the secondary alcohol group of epinephrine



**Actions and Uses**—Kephrine hydrochloride acts by constriction of the blood vessels. In comparison with epinephrine its action is less powerful, but the effects are more lasting. Kephrine hydrochloride is used only locally and will, as a rule, arrest capillary bleeding within two or three minutes. The hemostatic effects usually persist from one to two hours. As there is no appreciable absorption of kephrine hydrochloride into the blood stream, it does not have any noticeable effect on the blood pressure. Kephrine hydrochloride is not destroyed by blood alkali.

**Dosage**—Kephrine hydrochloride is marketed in the form of powder and suppositories, bandages and gauze impregnated with kephrine hydrochloride are also supplied. The selection of a suitable dosage form is governed by the anatomic or pathologic characteristics of the individual case.

#### Tests and Standards—

Kephrine hydrochloride occurs as a white odorless powder, freely soluble in water, soluble in alcohol, insoluble in ether. Its aqueous solution is neutral to litmus. Kephrine hydrochloride melts with decomposition at 238 to 240 C.

Dissolve about 0.5 Gm of kephrine hydrochloride in 25 cc. of water, add a very slight excess of ammonia water, collect the resultant precipitate on a filter, wash with water, and dry at 100 C. The filtrate from the precipitate, after evaporation of the excess of ammonia, deepens in color.

Dissolve about 0.02 Gm of kephrine hydrochloride in 20 cc of water, separate portions of 2 cc yield a canary yellow color with 1 cc of ammonium molybdate solution, which is not discharged on subsequent addition of 0.3 cc of dekanormal sodium hydroxide solution (distinction from epinephrine), a bluish purple color with 0.2 cc of a 1:100 sodium nitroprusside solution, 1 cc of sodium hydroxide solution and 0.2 cc of glacial acetic acid (distinction from salts of kephrine oxide solution). The filtrate from the precipitate, after evaporation of the excess of ammonia, deepens in color.

Accurately weighed, Incinerate about 0.5 Gm of kephrine hydrochloride, accurately weighed, the residue is not more than 0.1 per cent. Transfer about 0.25 Gm of kephrine hydrochloride, accurately weighed to a 500 cc Kjeldahl flask and determine the nitrogen content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists third edition page 20, art. 22. The amount of nitrogen is not less than 6.35 per cent nor more than 6.5 per cent.

when calculated to the dried substance. Transfer about 0.3 Gm. of kephrine hydrochloride, accurately weighed, to a suitable Erlenmeyer flask, add 100 cc. of water, previously boiled to remove carbon dioxide and titrate with tenth normal sodium hydroxide solution using phenolphthalein as an indicator; the amount of hydrogen chloride found corresponds to not less than 16.5 per cent nor more than 17 per cent, calculated to the dried substance. Transfer about 0.3 Gm of kephrine hydrochloride, accurately weighed, to a suitable glass stoppered Erlenmeyer flask, dissolve in about 20 cc. of water, neutralize with a diluted ammonium hydroxide solution, adding a very slight excess; place the flask and contents in a refrigerator at 5 C. and allow to stand for eighteen hours. Collect the precipitate on a tared Gooch crucible, wash with cold water followed by cold alcohol and ether, and dry to constant weight at 100 C. the percentage of methylamino acetatechol obtained corresponds to not less than 83 per cent, nor more than 86 per cent, calculated to the dried substance.

#### WINTHIOP CHEMICAL COMPANY, INC.

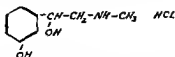
**Kephine Hydrochloride Powder:** Kephine hydrochloride 5 parts and tricalcium phosphate 95 parts.

**Kephine Hydrochloride Rectal Suppositories:** Kephine hydrochloride 3 parts, extract of belladonna 1 part, in 96 parts of a suppository base.

**Kephine Hydrochloride Bandage:** Bandages, 5 meters long and 1, 3, 5 and 8 centimeters wide, impregnated with kephrine hydrochloride, 1 Gm per 3,000 square centimeters.

**Kephine Hydrochloride Gauze:** Gauze impregnated with kephrine hydrochloride, 1 Gm. per 3,000 square centimeters.

of the laevo isomer of a synthetically prepared derivative of phenylethylamine having the formula  $C_6H_5.OH.CH(OH)CH_2NH_2.HCl$ . Neo-synephrine hydrochloride differs from synephrine tartrate in that (1) neo-synephrine hydrochloride is a salt of hydrochloric acid—synephrine tartrate is a salt of tartaric acid; (2) neo-synephrine hydrochloride is a *laevo* compound—synephrine tartrate is a *racemic* compound; and (3) the hydroxyl group of the nucleus in neo-synephrine hydrochloride is in the *meta* position—in synephrine tartrate it is in the *para* position.



**Actions and Uses.**—Neo-synephrine hydrochloride is a vasoconstrictor which is active when administered orally. It is more powerful in vasoconstrictive ability than synephrine tartrate, and possesses a relatively low toxicity. Applied to mucous membranes it causes contraction of the small blood vessels, thus reducing swelling and congestion of such membranes.

Neo synephrin hydrochloride may be useful in the symptomatic treatment of the nasal congestion accompanying disorders of the upper respiratory tract such as sinusitis vasomotor rhinitis and hay fever. In surgery the drug is useful for injection, in combination with a soluble local anesthetic, to retard the systemic absorption of the anesthetic and to prolong its action by local vasoconstriction. It may be injected alone for more general vasoconstrictor effects as a preliminary or supportive measure to combat acute hypotension in spinal anesthesia. It may be similarly employed in other acute hypotensive states due to peripheral circulatory collapse (vasomotor failure), but the present evidence does not justify its use in true shock where vasomotor activity is unimpaired and the fall in blood pressure is mainly the result of the loss in circulating blood volume. Its value as a cardiac stimulant is at present conjectural. It may also be used as a mydriatic in the eye preliminary to fundoscopic examination and in conjunction with cycloplegics in the detection of refractive errors and as an aid in the prevention or freeing of posterior synechiae and temporarily, as a vasoconstrictor to attempt to lower intraocular tension in certain cases of glaucoma when this effect is not counteracted by dilatation of the pupil.

**Dosage**—For topical application to the nasal mucous membrane the 0.25 per cent solution is ordinarily used. The 1 per cent solution diluted with an equal volume of physiologic solution of sodium chloride or Ringer's solution, may be used when a stronger preparation is desired. For surgical and dental anesthesia it may be diluted in the proportion of three to four drops of the 1 per cent solution to 10 cc of a 2 per cent procaine hydrochloride solution. For parenteral injection 0.1 to 1.0 cc of the 1 per cent solution. Initial dose should not exceed 0.5 cc (5 mg) and subsequent doses should not be administered at intervals less than 10 to 15 minutes. The intravenous dose when necessary should be about one tenth the subcutaneous or intramuscular dose. As a mydriatic, one or two drops of the 1 per cent solution or emulsion as a temporary vasoconstr

Preparation  
with butyr  
beforehand  
emulsion

alkaline solutions it may be sterilized by boiling

#### *Tests and Standards—*

Neo synephrine hydrochloride occurs as white odorless nonhygroscopic crystals possessing a bitter taste. It is readily soluble in water and alcohol. The aqueous solution is neutral to litmus paper. It melts between 139-141°C. The specific rotation  $[\alpha]_{25/D}$  ranges between -46.2 and -47.2.

Transfer 0.3 Gm of neo synephrine hydrochloride to a glass container dissolve in 3 cc of water add 15 drops of ammonia water and rub the glass container with a glass rod the base that separates when washed with cold water and dried melts at 170-171°C without decom

position Determine the nitrogen content of the base by the micro Dumas method: the nitrogen found is not less than 8.2 per cent nor more than 8.5 per cent. Dissolve 0.010 Gm of neo-synephrine hydrochloride in 1 cc. of water and add 1 cc. of copper sulfate solution (10 per cent) followed by 1 cc. of sodium hydroxide solution (20 per cent) a reddish purple color forms that is not extracted by ether. Dissolve 0.01 Gm. of neo-synephrine hydrochloride in 1 cc. of water and add 1 drop of ferric chloride (10 per cent). a permanent amethyst purple color develops. Dissolve 0.02 Gm. of neo-synephrine hydrochloride in 3 cc. of alcoholic potassium hydroxide solution, add 3 drops of chloroform and boil there is no odor of earhylamine (absence of primary amines). Dissolve 0.05 Gm. of neo-synephrine hydrochloride in 30-40 cc. of distilled water, a

1 cc. of barium chloride solution

sulfate). Dissolve 0.2 Gm of

of distilled water: the solution

when tested according to the U.

447) To 1 cc. of a solution

hydrochloride add 2 drops of

nitroprusside, 1 per cent, then 1 cc. of sodium hydroxide solution

followed by 0.6 cc (10 drops) of glacial acetic acid: the final solution should not be a deeper yellow than the same reagents, without the neo-synephrine hydrochloride (absence of corresponding ketone)

Dissolve about 0.2 Gm of neo-synephrine hydrochloride, accurately weighed, in 200 cc. of water, heat to boiling, add 4 cc of diluted nitric acid, followed by silver nitrate solution in slight excess; allow the container and mixture to stand for six hours, transfer to a Gooch crucible, wash well with diluted nitric acid (10 cc of diluted nitric acid diluted to 100 cc.), dry at 100 C., cool in a desiccator and weigh the chloride (Cl-) calculated from the silver chloride weighed is not less than 17.20 per cent nor more than 17.60 per cent. Heat about 0.2 Gm of neo-synephrine hydrochloride, accurately weighed, for twenty four hours, in an oven at 100 C: the loss is not more than 0.1 per cent Determine the nitrogen content by the micro Dumas method. the nitrogen found is not less than 6.7 per cent nor more than 7.0 per cent Transfer about 0.5 Gm of neo-synephrine hydrochloride, accurately weighed, to a platinum dish, ignite until constant weight is attained the ash is less than 0.1 per cent.

**NEO SYNEPHRINE HYDROCHLORIDE ONE PER CENT SOLUTION.** Transfer 10 cc of the solution to a beaker, evaporate the solution to dryness on a boiling water bath, extract the residue with three 15 cc. portions of boiling absolute isopropyl alcohol, evaporate the isopropyl alcohol to dryness on a boiling water bath, dry the extract in an oven at 100 C to constant weight. the residue is equal to not less than 0.95 per cent nor more than 1.05 per cent The melting point ranges between 138 and 140 C

Dissolve the residue in 3 cc of water, add 10 drops of ammonia water, rub the glass container with a glass rod filter the precipitate, wash with cold water on a porous plate the melting point is 169-171 C.

**NEO SYNEPHRINE HYDROCHLORIDE 3/4 PER CENT SOLUTION:** Follow the assay procedure described for the 1 per cent solution except use a 25 cc. sample.

## FREDERICK STEARNS & COMPANY

### Neo-Synephrine Hydrochloride Emulsion (Aromatic):

Neo-synephrine hydrochloride 0.25 per cent, sodium benzoate 0.4 per cent, camphor 0.07 per cent, menthol 0.052 per cent, oil of red thyme 0.17 per cent in a mineral oil and water emulsion containing acacia The product is preserved with chlorobutanol 0.5 per cent.

**Neo-Synephrine Hydrochloride Emulsion 1%, 15 cc bottle** Neo synephrine hydrochloride 1 per cent, sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia, preserved with chlorobutanol 0.5 per cent

**Neo-Synephrine Hydrochloride Emulsion 10%, 3 cc bottle** Neo synephrine hydrochloride 10 per cent sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia, preserved with sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent

**Solution Neo-Synephrine Hydrochloride, 0.25 per Cent 15 and 29.5 cc bottles** Neo synephrine hydrochloride 0.25 per cent, sodium benzoate 0.1 per cent and sodium chloride 0.8 per cent, in distilled water

**Solution Neo-Synephrine Hydrochloride, 1 per Cent 15 and 29.5 cc bottles** Neo synephrine hydrochloride 1 per cent, sodium benzoate 0.1 per cent, and sodium chloride 0.8 per cent, in distilled water

**Solution Neo-Synephrine Hydrochloride, 1 per Cent (for Parenteral Use).** A sterile solution of neo synephrine hydrochloride 1 per cent and sodium chloride 0.8 per cent, in distilled water

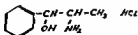
**Neo-Synephrine Hydrochloride Jelly** Neo-synephrine hydrochloride, 0.5 per cent, incorporated in a jelly-like bland base composed of tragacanth, chondrus, glycerin and water. Sodium benzoate 0.5 per cent is present as preservative. The product is supplied in collapsible tube containers

**Solution Neo-Synephrine in Ringer's Solution with Aromatics** 15 and 29.5 cc bottles Neo synephrine hydrochloride 0.25 per cent, sodium bicarbonate 0.0025 per cent, sodium sulfite not more than 0.11 per cent with camphor, menthol eucalyptus and Ringer's solution

U. S. patent ; 937,347 and 1,954,389 (April 10 1934 exp. res. April 10 1951) U. S. trademark 90142

## PROPADRINE HYDROCHLORIDE—d 1,1 phenyl 2

methyl group on the amino group is replaced by a hydrogen atom



**Actions and Uses**—Propadrine hydrochloride acts similarly to ephedrine. When applied locally, in the form of a 1 per cent aqueous solution or 0.66 per cent jelly, it produces constriction of the capillaries thereby shrinking the swollen mucous



membranes. It is said that its action is somewhat more prolonged than that of ephedrine. It is also claimed that the anxiety complex is not so apt to ensue with propadrine hydrochloride as with ephedrine.

**Dosage.**—As a spray or instillation, 1 per cent aqueous solution or application of 0.66 per cent jelly locally; orally, as 24 mg. capsule every two to four hours as indicated. Although no toxic effects have been noted, continued overdosage should be avoided as with other vasoconstrictors.

### Tests and Standards.—

as a white, crystalline powder, benzoic acid. It is freely soluble in ether, chloroform and benzene. Its melting point is 101-101.5 C.

Dissolve about 0.5 Gm. of propadrine hydrochloride in 25 cc. of water and add 5 cc. of a saturated solution of sodium carbonate. Cool in an ice bath and collect the resultant needle-shaped crystals on a filter paper, wash and dry at 80 C. the melting point of the  $\alpha$ -hydroxy- $\beta$ -amino-propylbenzene is 101-101.5 C.

Dissolve 0.05 Gm. of propadrine hydrochloride in 100 cc. of water. separate portions of 2 cc. yield a yellow color with 5 drops of a 9 per cent ferric chloride solution (distinction from ephedrine, naphrine, epinephrine), no precipitate with potassium mercuric iodide solution (Mayer's reagent) (distinction from benzedrine). To about 0.1 Gm. of propadrine hydrochloride in 5 cc. of water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution. no turbidity develops (sulfate).

Dry about 0.3 Gm. of propadrine hydrochloride, accurately weighed, to constant weight at 100 C. the loss in weight does not exceed 1 per cent. Incinerate about 0.3 Gm. of propadrine hydrochloride, accurately weighed. the residue does not exceed 0.3 per cent. Transfer about 0.2 Gm. of propadrine hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, page 23, art. 19: the amount of nitrogen is not less than 7.34 per cent, nor more than 7.52 per cent when calculated to the dried substance. Transfer about 0.2 Gm. of propadrine hydrochloride, accurately weighed, to a 400 cc. beaker and determine the chloride content according to the method as described in Methods of Analysis, fourth edition, page 131, art. 35: the amount of chloride found corresponds to not less than 18.85 per cent, nor more than 19.95 per cent when calculated to the dried substance.

### SHARP & DOHME, INC.

**Elixir Propadrine Hydrochloride:** Each 30 cc. contains propadrine hydrochloride 0.13 Gm in a menstruum composed of alcohol 16 per cent, glycerin, sucrose and water, flavored with oil sweet orange, fluidextract licorice, and oil ceylon cinnamon, and colored with carmoisin (certified) and caramel.

**Propadrine Hydrochloride Capsules:** 24 mg.

**Propadrine Hydrochloride Capsules:** 48 mg.

**Propadrine Hydrochloride Nasal Jelly, 0.66%:** Marketed in one-half ounce nasal tip collapsible tubes containing 0.66 per

cent propadrine hydrochloride with sodium chloride menthol thymol and oil of lavender in a water soluble base chlorbutanol 0.5 per cent is added as preservative

**Propadrine Hydrochloride Solution, 1%** An aqueous solution containing 1 per cent propadrine hydrochloride and made isotonic by the addition of 0.85 per cent sodium chloride, chlorbutanol 0.5 per cent is added as a preservative

**Propadrine Hydrochloride Solution, 3%** An aqueous solution containing 3 per cent propadrine hydrochloride and 0.5 per cent chlorbutanol as a preservative

U. S. patent 1,989,093 (Jan. 29, 1935 exp. res. 1952) Propadrine is a U. S. registered trademark, but the firm disclaims any proprietary rights to the name

### Anti Sympathomimetic Agents

Drugs exhibiting this action include preparations of ergot which are described in the chapter on exotics

### Parasympathomimetic Agents

#### ACETYL-BETA-METHYLCHOLINE

α  
n

actions of acetylcholine with little or none of the latter's nicotine effect. It exerts a depressant effect at the sinoauricular node, auricular musculature and auriculoventricular node and bundle of the heart and stimulates gastrointestinal peristalsis. The bradycardia induced by the drug is blocked by quinidine which also antagonizes its prolongation of auriculoventricular conduction. It also produces a general vasodilatation of blood vessels which are not known to be innervated by parasympathetic nerves with a subsequent fall in blood pressure. The drug may

tanously its actions appear to be more prolonged than those of acetylcholine although the effect on the heart rate and blood pressure persists for only a few minutes. Its intravenous injection is dangerous.

Crystalline water soluble salts of the base acetyl beta methyl choline are employed to produce the effects of the drug. The salts are more or less hygroscopic, and if this tendency is extreme as in the case of the chloride the crystals must be protected from atmospheric moisture until placed in solution.

Acetyl-beta-methylcholine chloride is therefore not suitable for oral administration in crystalline form but should be given in solution. The entire contents of containers of this salt should be put into solution immediately when these are once opened. Solutions of acetyl-beta-methylcholine chloride are fairly stable and will keep for at least two or three weeks. They are relatively stable to heat and may be refrigerated to delay mold growth.

The application of aqueous solutions of acetyl-beta-methylcholine chloride by the method of ion transfer (iontophoresis) to introduce this salt into the tissues by means of direct (galvanic) current is recognized as the best means to obtain the local effects of the drug on the extremities. General (systemic) effects are produced by this method but are less pronounced than when the drug is administered orally or by injection. The systemic effects produced in this way have not been observed to be of a serious or dangerous nature.

The following precautions should be observed in the administration of the drug: (1) Never administer intravenously because of the danger of cardiac arrest; (2) consider bronchial asthma, hyperthyroidism, coronary occlusion and any severe illness as contraindications; (3) avoid massage at the site of injection, except where this may be necessary to determine when a further injection is needed, and then only gently and with due caution; (4) advise recumbence during injection to avoid possible fainting; (5) the method of ion transfer (iontophoresis) should be employed only by those specially trained in such application and should not under any circumstances be used directly over ulcers or open wounds and only with care over scar tissue; extreme care is necessary to prevent burns by galvanism and the essentials of the "Safety Rules in Galvanism" outlined by Kovacs (Principles and Practice of Physical Therapy, vol III, pp. 10 and 11) should be followed in the administration of the drug by this method; (6) therapy by any method of administration is contraindicated when grave side reactions occur.

#### MECHOLYL BROMIDE

ethylcholine  
bromide —

*Actions and Uses*—The actions of mecholyl bromide are the same as for mecholyl chloride (see New and Nonofficial Remedies, 1942, p. 255), but because it is less hygroscopic than the latter salt, it is suitable for oral use in tablet form for the treatment of those conditions in which this route of administration of the drug is recognized. Claims for the use of mecholyl bromide other than by oral administration are not permissible and it should be kept in mind that for those skilled in the technic of ion transfer (iontophoresis) the local application of the chloride by this method is generally to be pre-

ferred in the treatment of chronic ulcers, scleroderma Raynaud's disease and other vasospastic conditions of the extremities, except possibly the management of vascular spasm from exposure to moderate cold

**Dosage**—Mecholyl bromide is administered in doses of 0.2 to 0.6 Gm (one to three tablets) two or three times daily, 0.05 to 0.1 Gm ( $\frac{1}{4}$  to  $\frac{1}{2}$  tablet) may be sufficient to overcome vascular spasm due to moderate exposure to cold, but in chronic ulcers scleroderma and Raynaud's disease the larger doses are required. With patients in whom a total daily dose of 2 Gm (10 tablets) of the drug is not effective, the oral method of treatment should be abandoned in favor of the use of mecholyl chloride by subcutaneous administration or local application by the method of ion transfer (iontophoresis)

### Tests and Standards—

Mecholyl bromide occurs as a white, crystalline very hygroscopic powder, possessing a slight fishy odor, readily soluble in water and alcohol, insoluble in benzene and ether. The aqueous solution is neutral to litmus. Mecholyl bromide melts at 147-149 C.

Dissolve about 1 Gm of mecholyl bromide in 10 cc of water, to a 1 cc portion add 1 cc of alcohol and 1 cc of sulfuric acid and heat in a steam bath the odor of ethyl acetate becomes perceptible to another 5 cc portion add 2.5 Gm of potassium hydroxide and heat (odor of trimethylamine is noticed), to the remaining portion add an excess of silver nitrate solution (a white curdy precipitate soluble in ammonia water results). Add 3 cc of a 20 per cent aqueous solution of sodium perchlorate to 2 cc of a 10 per cent solution of mecholyl bromide, shake thoroughly and cool in ice water, no precipitate is formed (acetylcholine). Moisten about 0.1 Gm of mecholyl bromide with a 5 per cent solution of platinum chloride, small rhombohedral plates are formed (distinction from acetylcholine chloride which forms needles and choline chloride which forms no crystals). Dissolve 0.2 Gm of mecholyl bromide in 2 cc of sulfuric acid, the solution is colorless (readily carbonizable substances).

Dry about 0.5 Gm of mecholyl bromide accurately weighed, to constant weight at 110 C, the loss in weight does not exceed 1.5 per

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Dissolve about 0.4 Gm of mecholyl bromide previously dried at 105 C to 110 C and accurately weighed in 15 cc of water in an

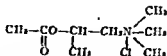
Transfer about 0.4 Gm of mecholyl bromide previously dried at 105 C to 110 C and accurately weighed to a 100 cc volumetric flask, dissolve in 50 cc of water, with agitation add 30 cc of tenth normal silver nitrate solution, add 5 cc of nitric acid and finally add water to final volume and mix thoroughly. Filter through a dry filter into a dry flask rejecting the first filterful, titrate 50 cc. of the filtrate with tenth normal ammonium thiocyanate solution using ferric alum as an indicator, the amount of bromine is not less than 32.9 per cent nor more than 33.5 per cent.

MENCK &amp; CO., INC.

**Mecholyl Bromide Tablets: 0.2 Gm.**

U. S. patent 2,040,146 (May 12, 1936; expires 1953). U. S. trademark 318,783.

MECHOLYL BROMIDE . . . . . methylcholine  
 chloride.—  
 giving the fol-



**Actions and Uses.**—Mecholyl chloride is useful in the treatment of selected cases of paroxysmal auricular tachycardia not responding to the usual therapeutic measures, by subcutaneous injection only, in the palliative local treatment of chronic rheumatoid (atrophic) arthritis by the method of ion transfer (iontophoresis) only, and in the treatment of chronic ulcers, Raynaud's disease, of the extremities,

(iontophoresis) but when the form of tachycardia employed for the prevention of attacks of paroxysmal auricular tachycardia the drug is inferior to quinidine. It is of no apparent value in the treatment of other forms of tachycardia in auricular fibrillation. The possibility of inducing transitory heart block, to be followed by resumption of normal rhythm, should be kept in mind. Claims for the use of the drug in the treatment of bladder dysfunction, abdominal distention, atonic constipation, pelvic inflammation, functional dysmenorrhea, atrophic rhinitis, glaucoma and hypertension are not warranted on the basis of existing clinical evidence (Also see preceding article, Acetyl-Beta-Methylcholine)

**Dosage**—Considerable variation in the oral dosage requirements is to be expected because mecholyl chloride is to some extent destroyed by the gastric juice. The therapeutically effective oral dose usually ranges from 0.2 to 0.5 Gm two or three times a day, administered by dissolving in a little water which may be added to milk to disguise the bitter taste. In overcoming vascular spasm due to moderate exposure to cold, oral doses of from 0.05 to 0.1 Gm have been found to be effective. In Raynaud's disease, scleroderma and ulcers the effective oral dose may be somewhat higher.

The subcutaneous dose should be limited to 0.01 Gm on the first injection to test the patient's tolerance. If well tolerated, the dose may be cautiously increased up to 0.025 Gm. This dose is usually adequate for injection when this method of administration is employed in the treatment of Raynaud's disease, scleroderma, chronic ulcers and other vasospastic conditions of the extremities. In paroxysmal auricular tachycardia from 0.02 to 0.04 Gm is injected subcutaneously. If a second

injection is required it is advisable to wait about ten to twenty minutes until the effect of the first has disappeared and then only after cautious gentle massage at the site of the first injection. Cumulative or overdosage effects may be quickly abolished by an injection of atropine sulfate 0.6 mg.

For application of mecholyl chloride by the method of ion transfer (iontophoresis) it is customary to use a 0.2 to 0.5 per cent (1:500 to 1:200) solution of the drug in distilled water. The solution is applied by moistening the positive electrode fabric which is placed over or near the part to be treated. The strength and duration of the galvanic current regulates the dosage and should always be applied gradually and within the point of comfortable tolerance by the patient. The patient should be instructed to report any sensation of excessive heat or burning. If this occurs the treatment should be stopped and an inspection made to determine if an electrode is improperly placed. The initial treatment should not exceed 5 to 10 milliamperes for thirty minutes. Subsequent treatments usually require from 25 to 30 milliamperes applied for twenty to thirty minutes. Each treatment should be restricted to a limited area such as one hand or one joint when several parts are involved. Three or four days is considered the most satisfactory interval between treatments. The number of treatments necessary to obtain results varies with the patient and with the type of lesion. In Raynaud's disease and scleroderma ten or more treatments may be necessary to secure improvement, in chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments, in varicose indolent and gangrenous ulcers treatments may be given daily at the start to promote granulation of tissue and then reduced after the first few treatments to two or three times a week. During treatments by ion transfer (iontophoresis) the patient should be covered and protected from drafts and for about thirty minutes after each treatment should remain quiet and be kept warm before being permitted to resume protected activity.

Idiosyncrasy to mecholyl chloride may result in difficulty in breathing. If this is noted the treatment should be stopped and the patient raised to a sitting position. If untoward symptoms do not subside, atropine sulfate should be given hypodermically at once.

#### *Tests and Standards—*

Mecholyl chloride occurs as a white crystalline very hygroscopic powder, possessing a slight odor, readily soluble in water and alcohol, insoluble in benzene and ether. The aqueous solution is neutral to litmus. Mecholyl chloride melts at 168 to 171 C.

Dissolve about 1 Gm. of mecholyl chloride in 10 cc. of water. To a 1 cc. portion add 1 cc. of alcohol and 1 cc. of sulfuric acid and heat in a steam bath (odor of ethyl acetate becomes perceptible). To another 5 cc. portion add 2.5 Gm. of potassium hydroxide and heat (odor of trimethylamine is noticed). To the remaining portion add an excess of silver nitrate solution (a white curdy precipitate soluble in ammonia water results). Add 3 cc. of a 20 per cent aqueous solution of sodium

perchlorate to 2 cc. of a 10 per cent solution of mecholyl chloride, shake thoroughly and cool in ice water: no precipitate is formed (acetylcholine). *Mecholyl chloride* (distinctly chloride, chloride in bonizable substances).

Dry about 0.5 Gm. of mecholyl chloride, accurately weighed, to constant weight at 110 C.: the loss in weight does not exceed 1.5 per cent. Incinerate about 0.5 Gm. of mecholyl chloride, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent. Transfer about 0.5 Gm. of mecholyl chloride, previously dried at 105 C. to 110 C., to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Methods of Analysis of the Association of Official Agricultural Chemists: the percentage of nitrogen is not less than 7 nor more than 7.25.

Dissolve about 0.4 Gm. of mecholyl chloride, previously dried at 105 C. to 110 C. and accurately weighed, in 15 cc. of water in an Erlenmeyer flask; add 40 cc. of tenth normal sodium hydroxide solution and heat on the steam bath for forty-five minutes; stopper and allow to cool, titrate the excess of sodium hydroxide solution with tenth normal hydrochloric acid using phenolphthalein as an indicator: the amount of acetyl ( $\text{CH}_3\text{CO}-$ ) is not less than 21.7 per cent nor more than 22.3 per cent.

Transfer about 0.4 Gm. of mecholyl chloride, previously dried at 105 C. to 110 C. and accurately weighed, to a 100 cc. volumetric flask, dissolve in 50 cc. of water, with agitation add 30 cc. of tenth normal silver nitrate solution, add 5 cc. of nitric acid, and finally add water to final volume and mix thoroughly. Filter through a dry filter into a dry flask, rejecting the first filterful; titrate 50 cc. of the filtrate with tenth-normal ammonium thiocyanate solution using ferric alum as an indicator: the amount of chloride ( $\text{Cl}-$ ) is not less than 17.9 per cent nor more than 18.4 per cent.

#### MERCK & Co., INC.

**Mecholyl Chloride (Crystals):** 1 Gm. and 10 Gm. bottles for the preparation of solutions for oral administration and for ion transfer (iontophoresis).

U. S. patent 2,040,146 (May 12, 1936, expires 1953) U. S. trade mark 318, 783.

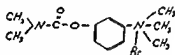
**Sealed Tube Mecholyl Chloride (Crystals):** 0.025 Gm. ampul for the preparation of solutions for subcutaneous injection

#### NEOSTIGMINE

it is considered that neostigmine preparations are used by subcutaneous and intramuscular injection since the neostigmine component is from four to six times as toxic as physostigmine when injected subcutaneously in the rabbit. Atropine is the antidote to neostigmine. Neostigmine preparations are used for the prevention of atony of the intestinal and bladder musculature and for the symptomatic control of myasthenia gravis. Their use for the prevention and treatment of intestinal and bladder atony is based on activity as a vagotonic agent; their anti-curare like action is the basis of application in the symptomatic treatment of myasthenia gravis. The drug is also credited with mild laxative action but its use solely for that purpose is not advisable.

Neostigmine is available only in the form of its salts.

**NEOSTIGMINE BROMIDE — U S P —** Prostigmine Bromide— When dried for 6 hours at 100° C contains not less than 98 per cent of  $C_{12}H_{19}BrN_2O$  U S P



For description and standards see the U S Pharmacopeia under Neostigmine Bromidum and Tabellae Neostigmine Bromidi.

**Action and Uses**—See Neostigmine. Neostigmine bromide is used for the oral treatment of myasthenia gravis. The bromide is used in the oral tablet form as it is comparatively non-hygroscopic.

**Dosage**—0.015 Gm. three times daily. If necessary the dose may be cautiously increased to 0.03 Gm. three times daily.

HOFFMANN LA ROCHE INC.

Prostigmine Bromide Tablets 0.015 Gm.

U S patent 1,905,990 (April 25, 1933; expires 1950) U S trade mark 293,889.

**NEOSTIGMINE METHYLSULFATE — U S P —** Prostigmine Methylsulfate— When dried at 100° C for 6 hours contains not less than 98 per cent of  $C_{12}H_{19}NO_2S$  U S P

For description and standards see the U S Pharmacopeia under Neostigmine Methylsulfas and Injectio Neostigmine Methylsulfatis.

**Actions and Uses**—See Neostigmine.

**Dosage**—Prevention of postoperative distention: small doses of the 1:4,000 solution are administered subcutaneously or intramuscularly at frequent intervals. Injections are begun twenty-four hours before the operation if feasible; otherwise as soon



as possible, and repeated in 1 cc. doses every four to six hours until the second or third postoperative day. Treatment of postoperative distention: usually one or two ampuls of the 1:2,000 solution, as required, are administered subcutaneously or intramuscularly. Experimental use in the treatment of myasthenia gravis: only one ampul of the 1:2,000 solution is administered initially, the size and interval of the subsequent doses to be given as indicated by the degree and duration of the response to the initial dose. The course of treatment usually consists of from one to four ampuls (from 0.5 to 2 mg. of neostigmine methylsulfate).

HOFFMANN-LA ROCHE, INC.

Ampuls Solution Prostigmine Methylsulfate 1:2,000:  
1 cc.

Ampuls Solution Prostigmine Methylsulfate 1:4,000:  
1 cc.

U. S. patent 1,905,990 (April 25, 1933; expires 1950) U. S. trade mark 293,889.

## Anti-Parasympathomimetic Agents

### ATROPINE DERIVATIVES AND ANALOGUES

#### Synthetic Mydriatics

The usefulness of atropine is somewhat diminished by the fact that it affects, simultaneously, so many organs; on the eye its effects continue much longer than is in many cases desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine; eucatropine is a combination of mandelic acid and a base similar to that contained in beta-eucaine.

**EUCATROPINE HYDROCHLORIDE.**—U. S. P.—Euphthalmine Hydrochloride—"When dried over sulfuric acid for 4 hours, contains not less than 86 per cent and not more than 89 per cent of eucatropine ( $C_{17}H_{21}O_3N$ )."  
U. S. P.

For description and standards see the U. S. Pharmacopeia under Eucatropinae Hydrochloridum.

**Actions and Uses**—Eucatropine hydrochloride produces prompt mydriasis free from anesthetic action, pain, corneal irritation or, in normal individuals, increase in intra-ocular tension. It should be noted, however, that eucatropine hydrochloride shares with other mydriatics the hazard of precipitating glaucoma in anatomically predisposed individuals. It has little or no effect on accommodation, and such effect as it has dis-

appears more rapidly than that of atropine, cocaine, homatropine, etc. In its effects on the general system, eucatropine hydrochloride, very closely resembles atropine. It is useful as an aid in ophthalmoscopic examination in place of atropine, homatropine, etc.

**Dosage**—From 2 to 3 drops of from a 5 to 10 per cent solution, according to the age of the patient and the nature of the case, are instilled into the eye.

SCHERING & GLATZ, INC.

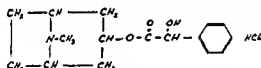
Euphthalmine Hydrochloride (*Powder*) 0.5 Gm and 5 Gm

U. S. patent 663,754 (expired) U. S. trademark 35,541

WERNER DRUG & CHEMICAL CO.

Eucatropine Hydrochloride (*Powder*)• bulk 0.5 Gm, 1 Gm and 5 Gm

**HOMATROPINE HYDROCHLORIDE.**—Homatropinae Hydrochloridum.— $C_{16}H_{19}O_3NHCl$ —The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid.



**Actions and Uses**—Homatropine hydrochloride is given for the same indications as the hydrobromide.

**Dosage**—It is applied to the eye in 1 per cent solution.

**Tests and Standards**—

Homatropine hydrochloride occurs as small white crystals soluble in water and alcohol and melting at from 216 to 217° C.

The color test for the identification of homatropine hydrochloride and the tests showing the absence of impurities should agree with those described in the U. S. Pharmacopoeia under homatropine hydrobromide.

MERCK & CO., INC.

Homatropine Hydrochloride (*Crystals*): bulk

**NOVATROPINE.**—Homatropinemethylbromide —  $C_{16}H_{21}O_3NCH_3Br$ —The methylbromide of the alkaloid homatropine.

**Actions and Uses**—Novatropine is proposed for use in the treatment of gastrointestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic.

**Dosage**—Adults: one or two tablets three times daily before meals; children and infants: according to age.

**Scopolamine Hydrobromide Powder:** 0.065 Gm, 0.3 Gm and 1 Gm. vials.

**SCOPOLAMINE STABLE.**—Scopomannit.—An aqueous solution of pure scopolamine hydrobromide, protected against decomposition by the addition of 10 per cent of mannite

**Actions, Uses and Dosage.**—The same as those of scopolamine hydrobromide-U. S. P

**Tests and Standards.**—

Scopolamine stable-Roche is prepared by dissolving in an aqueous 10% solution of mannite freshly manufactured scopolamine hydrobromide having an optical activity of  $[\alpha]_{\text{D}}^{15} \approx -26.0^{\circ}$  (determined in an aqueous solution containing the equivalent of 4.5 Gm of anhydrous scopolamine hydrobromide in 100 cc. at a temperature of 15 C. in a 100 millimeter tube). The melting point of scopolamine hydrobromide is 195 C.

That scopolamine stable Roche contains all of its scopolamine in an undecomposed state may be determined by comparing its action with that of a freshly prepared solution of scopolamine hydrobromide. For this purpose the manufacturers recommend the method of Langer, in which the frog heart is stopped by muscarine, or, better, by pilocarpine, and the beat is reestablished by the addition of scopolamine, which is antagonistic to both muscarine and pilocarpine.

**HOFFMANN-LA ROCHE, INC.**

U. S. trademark 103,288 and 103,289

**Ampule Solution Scopolamine Stable:** 0.3 mg. in 1 cc  
Each cubic centimeter contains 0.3 mg. of scopolamine hydrobromide in a 10 per cent aqueous solution of mannite.

**Ampule Solution Scopolamine Stable:** 0.6 mg. in 1 cc  
Each cubic centimeter contains 0.6 mg. of scopolamine hydrobromide in a 10 per cent aqueous solution of mannite

## CHAPTER VII

### CARDIOVASCULAR AGENTS

#### Digitalis and Digitalis-like Principles and Preparations

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. *Digitalis strophanthus* and squill have been investigated far more than the others and we are much better informed concerning their actions from them are derived nearly all the active principles and proprietary preparations of the group which have been included in N. N. R.

**Cardiac Action**—The cardiac action of the individual drugs of the group is similar. They all act directly on heart muscle to increase its systolic force. The margin between therapeutic and toxic actions on the heart is believed by some to differ for different substances although the weight of evidence indicates that the margin of safety does not differ. In patients with auricular fibrillation they all slow the heart rate by a combination of a direct action on the heart muscle and an indirect vagal action. The larger the dose the more pronounced the direct action. The proportion of these two actions is similar for the different members of the whole group.

Differences exist chiefly in relation to their absorption from the gastrointestinal tract, their speed of elimination and their local emetic action. Their potencies differ and difficulties arise from faulty standardization.

**Standardization**—There are various methods for the standardization of this group of drugs involving the use of several species of animals: the frog, the guinea pig, etc. The U. S. Pharmacopeia 12th Revision requires that digitalis be standardized against the U. S. P. Digitalis Reference Standard (1942) by the official cat method which involves intravenous injection into cats until death occurs by cardiac arrest. The available evidence indicates that the cat method yields results more nearly applicable to man than those of the frog method. The Standard preparation and the unknown are similarly injected into groups of animals and the average fatal doses of the two are compared. The unknown is then adjusted so that 0.1 Gm. has the potency of 0.1 Gm. of the Standard or 1 U. S. P. Digitalis Unit. Since the U. S. P. Digitalis Unit is the result of an assay by the cat method and represents an improved technique in bioassay, the expression of potency in U. S. P. Digitalis Units is preferable to the older expression in terms of cat units.

In the case of digitalis leaf and the tincture, the results of comparison by means of the cat method agree fairly satisfactorily with similar comparisons in humans to whom the drugs

are given by oral administration, but there is less agreement in the case of purified materials because of wide differences in their absorption from the gastrointestinal tract, and the intravenous method does not distinguish absorbable from nonabsorbable material. Hence a U. S. P. Unit of different specimens of the *Digitalis* Leaf or Tincture *Digitalis* may be counted upon to produce substantially similar results when given orally to man (although there are some exceptions), but not so in the case of purified materials.

By direct testing it has been found that 1 U. S. P. *Digitalis* Unit is equivalent approximately to 1.3 "cat units," using the cat method technique of the Pharmacopeia.

*Differences in Emetic Action*—The digitalis principles are irritant to mucous membranes and subcutaneous tissues. When given in large doses, the local irritation in the gastro-intestinal tract may be sufficient to cause nausea and vomiting within several minutes to an hour or two. These drugs, however, are rarely administered in such doses, and when given in the usual smaller doses the local irritant action is insufficient to cause nausea or vomiting. The nausea or vomiting which follows the customary doses of digitalis is due to a systemic action after absorption and represents a toxic symptom. The seat of this action is the vomiting center through the heart. The emetic action is roughly proportional to the cardiac effects of the various members of the group and when this undesired action is induced, it cannot be avoided by changing the mode of administration or by resorting to other members of the group. In such a case, the patient is overdigitalized and there is need for reducing the size of the dose.

*Differences in Absorption*—Digitalis contains a mixture of glycosides, some of which are rapidly, and others poorly absorbed from the gastrointestinal tract. After an oral dose only about one fifth of the potent materials produce a systemic action, as shown by the fact that it requires only about one-fifth as much for intravenous as for oral administration to produce the same results. Digitaline Nativelle (digitoxin) is almost completely absorbed, whereas other fractions may not be absorbed at all. The potent principles of *strophanthus* are so poorly absorbed from the gastrointestinal tract that they are undesirable for oral administration and are used chiefly by intramuscular or intravenous injection in small doses.

*Differences in Cumulative Action*—All the digitalis bodies in common use are cumulative. Not all show the same degree of cumulation, however, due to the fact that some are more rapidly eliminated than others. The cumulative action is especially pronounced in the case of digitalis leaf and digitaline Nativelle (digitoxin). It is much less in the case of *strophanthus* and *strophanthin*.

*Intravenous Use*—The frequency of repetition of the intravenous dose of different digitalis preparations varies widely even with those of equal potency depending on several factors especially on difference in persistence of action. The physician must learn the proper intravenous dose of any preparation of digitalis which he employs.

### *a Digitalis Principles and Preparations*

The disadvantages of all the drugs of the digitalis group

local irritant action of the large amount of nonabsorbable glycosides. However, the chemistry of digitalis and the other members of the group is still imperfectly understood and none of the pure glycosides is available on a commercial scale in a state sufficiently uniform to make it possible to dispense with biological standardization. Several glycosides are available in a fairly high degree of purity such as strophanthin ouabain digitaline nativele (digitoxin). Many preparations however are mixtures of glycosidal materials such as digitolin or digalen.

*Proprietary Digitalis Preparations*—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles or of purified extracts of digitalis and that they are devoid of certain disadvantages possessed by the preparations of the U. S. Pharmacopeia.

It may be said at once that there is no proof that the proprietary preparations can be used to greater advantage than digitalis and its galenicals in the majority of cases of heart disease. The Council therefore urges on clinicians the necessity of acquiring skill in the use of digitalis materials by the careful observation of a very few members of the group rather than to try to use without discrimination the large number of preparations which are offered.

**DIGITALIS**—Foxglove—Digitalis is the dried leaf of *Digitalis purpurea* Linné (Fam. *Scrophulariaceae*). The potency of Digitalis shall be such that when assayed as directed 0.1 Gm shall be equivalent to not less than 10 U. S. P. Digitalis Unit. U. S. P.

*Note*—When Digitalis is prescribed *Digitalis Pulverata* is to be dispensed U. S. P.

For description and standards see the U. S. Pharmacopeia under *Digitalis Capsulae*, *Digitalis*, *Digitalis Pulverata*, *Injectio Digitalis*, *Tabellae Digitalis* and *Tinctura Digitalis*.

*Actions, Uses and Dosage*—See Useful Drugs.

**ABBOTT LABORATORIES**

**Capsules Digitalis Leaf:** 0.1 Gm., 1 U. S. P. unit.

**BURROUGHS WELLCOME & Co., INC.**

**Tabloid Digitalis Leaf:** 32 mg., 65 mg. and 97 mg

**Tincture Digitalis:** 30 cc., 120 cc. and 480 cc. bottles

**DAVIES, ROSE & COMPANY, LTD.**

**Pills Digitalis Leaves:** 0.1 Gm., 1 U. S. P. unit

**THE DRUG PRODUCTS COMPANY, INC.**

**Pulvoids Digitalis Folium:** 32 mg. ( $\frac{1}{3}$  U. S. P. unit); 50 mg. ( $\frac{1}{2}$  U. S. P. unit); 0.1 Gm. (1 U. S. P. unit).

**ENDO PRODUCTS, INC.**

**Tablets Digitalis:** 50 mg. ( $\frac{1}{2}$  U. S. P. unit) and 0.1 Gm (1 U. S. P. unit) (enteric coated). The tablets are first coated with a white shellac and then sugar-coated green

**CHARLES C. HASKELL & Co., INC.**

**Whole Leaf Tablets Digitalis:** 1 cat unit as determined by the Hatcher-Brody method

**LEONIE LABORATORIES, INC.**

**Tablets Digitalis Whole Leaf:** 0.05 Gm,  $\frac{1}{2}$  U. S. P. unit; 0.10 Gm, 1 U. S. P. unit, and 0.2 Gm, 2 U. S. P. units

**McNEIL LABORATORIES, INC.**

**Capsules Digitalis Duo-Test:** 65 mg ( $\frac{2}{3}$  U. S. P. unit)

**Capsules Digitalis Duo-Test:** 0.1 Gm. (1 U. S. P. unit in black capsules).

**Tablets Digitalis Duo-Test:** 32 mg ( $\frac{1}{3}$  U. S. P. unit in plain tablets).

**Tablets Digitalis Duo-Test:** 65 mg ( $\frac{2}{3}$  U. S. P. unit) and 0.1 Gm. (1 U. S. P. unit) dispensed in plain and coated tablets

**THE MALTBIE CHEMICAL COMPANY**

**Capsules Digitalis Powder:** 32 mg. ( $\frac{2}{3}$  U. S. P. unit in blue capsules) and 0.1 Gm. (1 U. S. P. unit in blue capsules)

**THE WM. S. MERRELL COMPANY**

**Tablets Digitalis:** 0.1 Gm (1 U. S. P. unit).

**Tincture Digitalis:** 295 cc., 108 cc., 480 cc. and 960 cc bottles

**PITMAN-MOORE COMPANY**

**Pulvo-Caps Digitalis:** 0.1 Gm (1 U. S. P. unit) and 65 mg ( $\frac{2}{3}$  U. S. P. unit)

Tablets Digitalis 32 mg ( $\frac{1}{2}$  U S P unit) and 0.1 Gm. (1 U coated)

**Tincture Digitalis** 120 cc 25¢

SHARP &amp; DOHME, INC.

**Capsules Digitalis 01 Gr. ( )**

Tablets Digitalis 01 Gm.  $\frac{1}{100}$

### Tincture Digitalis

E R SULLIVAN &amp; SONS

**Tablets Digitalis** 1 l. c.

THE UPJOHN COMPANY

**Ampoule Sterile Saline**

10 cc Each cubic centimetre  
unit and alcohol 10 per  
sterile phosphate buffer

UPSHER SMITH Co

## Capsules Digitales

(% U S P M)

### Tablets Digit

(1/3 U S F \)

### Tincture T

## THE W19

Table

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digitalis leaves are extracted with distilled water is then treated with alcohol precipitated acetate and filtered. The filtrate after neutralization is filtered and concentrated under high vacuum at a temperature not exceeding 40°C. The solids which separate through the foregoing concentration and dried under a high vacuum at a temperature not exceeding 40°C. The residue dissolved in methyl alcohol the filtrate treated with chloroform separated from the aqueous solution the residue dissolved in methyl alcohol. The oil has been separated from the chloroform solution mixture of ether two parts and benzene one part. The extract is concentrated under high vacuum at low temperature. The remaining residue dissolved in methyl alcohol. The alcohol solutions are mixed decolorized with charcoal and concentrated under a high vacuum to a dry residue which contains

almost colorless and odorless with a slightly bitter

water methyl  
um ether

	gm ether
" "	Gm in water of pure alcohol

1	•	of pure glacial (ferrie sulfate of the Boreas
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digifolium in 5 cc. of solution A and layer this solution care.

5 cc of solution B at the point of contact a dark band the lower layer assumes a red color and the upper layer a green color on standing the bluish green layer turns to indigo



*Preparation—*

The dried and finely powdered leaves of digitalis are extracted with diluted alcohol, then the extract is mixed with lead acetate solution in order to remove chlorophyll and resins, and filtered. From this filtrate the excess of lead is precipitated with sodium sulfate, and the alcohol distilled off *in vacuo*. From the remaining aqueous solution, the active derivative of digitalis contained in digalen is extracted by ethereal solvents and precipitated afterwards in an amorphous condition according to a special secret method. The several dosage forms are standardized by the intravenous cat method.

*Tests.—*

Digalen is a colorless or slightly yellowish liquid of an agreeable aromatic odor with a sweet taste which subsequently becomes bitter.

The active derivative contained in digalen is an amorphous, white or slightly yellow powder. It is stated to have a solubility five times as great as that of crystallized digitoxin. It is stated to dissolve readily in alcohol and chloroform, and less readily in ether. It has an intensely bitter taste and causes violent sneezing, when introduced into the nose.

To 2 cc. of digalen add a few drops of diluted acetic acid and extract with chloroform. Evaporate the chloroform extract and dissolve the residue in about 2 cc. of glacial acetic acid containing a trace of ferric chloride. To this solution add strong sulfuric acid without mixing so as to form a separate layer: a brown ring forms between the two layers which becomes broader after some hours and expands toward the top in a blue green to black shade, and toward the bottom in a reddish brown one. The acetic acid finally acquires a dark green blue color.

**HOFFMANN-LAROCHE, INC.**

**Ampul Solution Digalen Injectable:** 2 cc. Each 2 cc represents 1 cat unit, in 8 per cent alcohol, equivalent in potency to approximately 81 mg. U. S. P. Digitalis Reference Standard (1942)  $\approx$  0.8 U. S. P. XII Digitalis Unit.

**Solution Digalen:** 30 cc. vials. Each 1 cc. represents 1 cat unit, in 26 per cent alcohol, equivalent in potency to approximately 81 mg. U. S. P. Digitalis Reference Standard (1942)  $\approx$  0.8 U. S. P. XII Digitalis Unit.

**Tablets Digalen:**  $\frac{1}{2}$  cat unit and 1 cat unit, respectively equivalent in potency to 40 mg. U. S. P. Digitalis Reference Standard (1942)  $\approx$  0.4 U. S. P. XII Digitalis Unit, and 81 mg. U. S. P. Digitalis Reference Standard (1942)  $\approx$  0.8 U. S. P. XII Digitalis Unit.

U. S. trademarks 43,593 and 83,738

**DIGIFOLIN.**—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf. It is standardized by the intravenous cat method of Hatcher and Brody (*Am J. Pharm* 82:360, 1910).

**Actions and Uses.**—The same as those of digitalis.

**Dosage.**—In the majority of cases in which digitalis therapy is indicated, the oral administration of 0.1 Gm in the form of tablets, or of 1 cc of digifolin liquid four times daily until the desired therapeutic effects or minor toxic symptoms appear. In cases in which the patient has received no digitalis during the preceding two weeks and it is desired to use the massive

dose method digifolin tablets or digifolin liquid, in the proportion of the former representing 0.7 Gm of digitalis or 8 cc of the latter per 45.4 Kg of the patient's body weight may be employed as the initial dose. If neither clinical improvement nor toxic signs have appeared in six hours, a second dose may be given, one-half the size of the initial one, and at the

pounds of the patient's weight. The intravenous dose of digifolin recommended is 0.03 cc of the contents of the ampule per pound of body weight in patients who have received no digitalis medication during the preceding two weeks. In the absence of therapeutic effects or signs of digitalis poisoning at the expiration of two hours, 0.0176 cc per Kg of body weight may be injected, and further doses of 0.0176 cc per Kg of body weight may be injected intravenously at two hour intervals until improvement occurs, poisoning becomes apparent or a total dosage of 0.132 cc per Kg of body weight has been reached. Under no circumstances should this dosage be exceeded in seriously ill patients.

#### *Preparation—*

Dried and finely ground digitalis leaves are extracted with distilled water. The neutralized filtrate is then treated with alcohol, precipitated with a solution of lead acetate and filtered. The filtrate, after the removal of the lead and neutralization, is filtered and concentrated to a certain volume in a high vacuum at a temperature not exceeding 30 C. The active principles which separate through the foregoing concentration are collected and dried under a high vacuum at a temperature of 40 C. It is then dissolved in methyl alcohol, the filtrate treated with chloroform and the chloroform separated from the aqueous solution, distilled off and the residue dissolved in methyl alcohol. The aqueous solution which has been separated from the chloroform solution is treated with a mixture of ether two parts and benzene one part; the ether-benzene extract is concentrated under high vacuum at low temperature and the remaining residue dissolved in methyl alcohol. The several methyl alcohol solutions are mixed, decolorized with charcoal and concentrated under a high vacuum to a dry residue, which constitutes digifolin.

#### *Tests—*

Digifolin is almost colorless and odorless, with a slightly bitter taste. It is an amorphous brownish powder, soluble in water, methyl alcohol and ethyl alcohol, insoluble in ether and petroleum ether.

Prepare two solutions: (A) Dissolve ferric sulfate, 5 Gm in water, 100 cc, filter and add 5 cc of the filtrate to 500 cc of pure glacial acetic acid; (B) add 5 cc ferric sulfate solution (ferric sulfate 5 Gm in water, 100 cc) to 500 cc pure sulfuric acid. Dissolve a trace of digifolin in 5 cc. of solution A and layer this solution carefully on 5 cc of solution B. At the point of contact, a dark band appears, the lower layer assumes a red color and the upper layer a bluish green color; on standing the bluish green layer turns to indigo blue.

## CIBA PHARMACEUTICAL PRODUCTS, INC.

**Ampule Solution Digifolin:** 2 cc. Each 2 cc. contains digifolin equivalent to 0.1 Gm., 1 cat unit, of digitalis leaves. The solution contains neither alcohol nor glycerin.

**Digifolin Liquid:** Each 1 cc. contains digifolin equivalent to 0.1 Gm., 1 cat unit, of digitalis leaves. It contains 12 per cent alcohol.

**Tablets Digifolin:** Each tablet contains digifolin equivalent to 0.1 Gm., 1 cat unit, of digitalis leaves.

U S trademark 449,819

**DIGILANID.**—A mixture of the isomorphous crystallized cardio-active glucosides lanatosid-A ( $C_{40}H_{70}O_{16}$ ), lanatosid-B ( $C_{40}H_{70}O_{16}$ ) and lanatosid-C ( $C_{40}H_{70}O_{16}$ ), obtained from the leaves of *Digitalis lanata*. The three components are present in the mixture in the proportions in which they occur in the crude drug, namely about 47 per cent lanatosid-A, 16 per cent lanatosid-B and 37 per cent lanatosid-C.

**Actions and Uses.**—The actions and uses are closely similar to those of digitalis U S. P.

**Dosage.**—The average oral daily dose is from two to four tablets or from 2 to 4 cc. of the liquid until the therapeutic effects are induced or until minor toxic symptoms appear, after which a maintenance dose of about half that just given will

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tration of larger oral doses or the intramuscular or intravenous injection of suitable doses. These demand the careful observation of the proper technic, which is described in the circular which accompanies the package.

#### Preparation —

The dry leaves of *Digitalis lanata* are ground with ammonium sulfate, wet with water and extracted with ethyl acetate. The filtered extract is evaporated to dryness *in vacuo*, treated with ether and allowed to stand until the mass becomes solid. The ether is poured off and the residue digested with ether. The dried residue from the operation is pulverized, dissolved in methyl alcohol and treated with lead hydroxide in water. The resultant mixture is neutralized and filtered, the filtrate is concentrated *in vacuo* and the precipitated glucosidal mixture filtered. The residue is recrystallized from methyl alcohol and water mixtures.

Digilanid crystallizes from aqueous methanol solutions in flat prisms which contain 6 per cent (2 mol) of methanol and 3.5 per cent (2 mol) of water. The material takes on a high vacuum. The product is

#### Tests and Standards —

Air dried digilanid occurs as a white, odorless powder, possessing a bitter taste, soluble in methanol, 1 in 20, very slightly soluble in water, 1 in 10,000 and insoluble in ether. Digilanid, when heated rapidly, melts with decomposition above 245 C.

Transfer 0.002 Gm of digilanid to a 15 cm test tube and add 4 cc of glacial acetic acid and one drop of ferric chloride solution. Add from a pipet 4 cc of sulfuric acid to underlay the acetic acid solution and allow to stand one hour: a blue color appears in the upper zone (*digitoxose*) and a violet brown in the lower zone (*mixture of aglucones*). Transfer about 0.02 Gm of digilanid to a 10 cm test tube and add 1 cc each of water, methanolate precipitation or coloration substances). Transfer about 0.02 Gm of digilanid to a 10 cm test tube and add 2 cc of methanol, 2 cc of ferric chloride solution and heat for 10 minutes (reducing sugars).

Transfer about 0.2 Gm of digilanid dried under vacuum and accurately weighed to a 10 cc volumetric flask and make up to volume with ethanol. Mix, transfer to a 2 dm polarizing tube and observe the angular rotation using sodium light at 25°C. The specific rotation  $[\alpha]_D^{25}$  is not less than +32.0 and not more than +33.8.

Transfer about 0.2 Gm of digilanid dried under vacuum and accurately weighed to a 150 cc glass stoppered Erlenmeyer flask and cautiously add 40 cc of methanol and 20 cc of tenth normal sodium hydroxide. Stopper the flask and allow to stand seventy-two hours. To a similar flask add 40 cc of ethanol and 20 cc of tenth normal sodium hydroxide, stopper and allow to stand seventy-two hours. Titrate both solutions with tenth normal hydrochloric acid using phenolphthalein as indicator. The volume of tenth normal sodium hydroxide required by 1 Gm of digilanid is not less than 20.0 and not more than 23.0 cc.

Transfer about 0.2 Gm of digilanid dried under vacuum and accurately weighed to a 250 cc separator, add 100 cc of chloroform, 20 cc of methanol and 100 cc of water and shake at 25°C for one minute. Separate the layers and evaporate each in vacuo to dryness. Wash the residues into tared weighing bottles with methanol and again evaporate to dryness in vacuo at 55°C and weigh. The weight of the residue from the chloroform divided by the sum of the weights of the residues is not less than 0.60 and not more than 0.63.

#### SANDOZ CHEMICAL WORKS, INC.

**Ampule Solution Digilanid 2 cc (For Intramuscular Use)** Each ampul contains 0.4 mg of digilanid equivalent to 1.2 cat units of digitalis.

**Ampule Solution Digilanid 4 cc (For Intravenous Use)** Each ampul contains 0.8 mg of digilanid equivalent to 2.4 cat units of digitalis.

**Solution Digilanid 30 cc vials** Each 1 cc contains 0.33 mg of digilanid equivalent to 1 cat unit of digitalis.

**Suppositories Digilanid 0.5 mg (1.5 cat units)**

**Tablets Digilanid 0.33 mg (1 cat unit)**

U. S. patents 1,923,490 (Feb. 19, 1931, expires 1948) and 1,923,491 (Aug. 22, 1931, expires 1948). U. S. trademark 291,301.

**DIGIPOTEN**—A mixture of the digitalis glucosides in soluble form, diluted with milk sugar to give the preparation an activity equal to that of digitalis of standard quality as determined by the U. S. Pharmacopeia. It is standardized by the U. S. P. intravenous cat method. Activity is expressed in U. S. P. digitalis units. It is virtually free from digitosaponin.

**Actions and Uses.**—Digipoten has the same activity as digitalis leaf of good quality and may be used as is the official drug with respect to indications and dosage.

**Dosage.**—The same as that of digitalis.

**Preparation.**—

Digipoten is prepared by extracting digitalis leaves with diluted alcohol, the alcohol being removed by distillation *in vacuo*, the resulting extract filtered, and the filtrate precipitated with tannin. The precipitated tannates of the glucosides are washed with water, and the glucosides are liberated in the usual manner. The resulting green brittle powder is triturated with sufficient milk sugar to reduce the activity of the finished product to the standard.

**Tests.**—

Digipoten is a pale green powder, possessing the characteristic bitter taste of digitalis. It is soluble in water and in 25 per cent alcohol.

On ignition it leaves no appreciable amount of ash. If 0.1 Gm. of digipoten is dissolved in 2 cc of glacial acetic acid containing a trace of ferric chloride and underlaid with concentrated sulfuric acid, there appears at first a brownish zone, changing to red, and finally the upper layer changes to a dark green (*digitoxin*).

#### ABBOTT LABORATORIES

Digipoten Capsules: 0.1 Gm, 1 U. S. P. unit

Tablets Digipoten: 0.05 Gm, ½ U. S. P. unit.

**DIGITALIN, "GERMAN."**—*Digitalinum Germanicum*.—A mixture of glucosides obtained from digitalis seeds according to the process of Walz, and consisting largely of digitonin, with true digitalin and other glucosides.

**NOTE.**—Digitonin is given as a synonym for crystallized digitalin by some manufacturers, and it is to be observed particularly that this is quite different from "true digitalin" or the "crystalline digitaline" of the French Pharmacopœia.

**Actions and Uses.**—These are similar to those of digitalis.

**Dosage.**—What has been said of the uncertainty of dosage of true digitalin must obviously apply with even greater force to "German" digitalin, since the activity of the latter probably depends mainly on the true digitalin that it contains. The dose of "German" digitalin was formerly given as 0.001 to 0.002 Gm. maximum dose 0.004 Gm, with a maximum per day of 0.002 Gm. Many clinicians, however, have used very much larger doses without ill effects, and the relative activity of certain specimens of the "German" digitalin and other members of the group would seem to indicate that such specimens of "German" digitalin might be given safely in daily doses of a grain, or possibly more.

As "German" digitalin (so-called *digitalinum purum*) is a mixture of very powerful active principles, the proportion of which may vary with changes in the manipulations, it is important that the directions for its preparation should be carefully followed, and caution should be exercised to purchase only such products as the manufacturers can guarantee to have been made with the necessary care.

**Preparation —**

Digitalis seeds are extracted with alcohol the alcohol driven off, and the extract diluted with water and purified by precipitation with lead acetate. The filtrate is freed from lead by sodium phosphate. From the liquid thus purified the digitalin bodies are precipitated with tannic acid and the tannate well washed with water and decomposed with lead or zinc acetate. The digitalin thus separated is taken up in alcohol the latter carefully distilled off and the residue washed with ether as long as it takes up anything. The digitalin purified in this way is dried at a low temperature and finely powdered. (Hager's Handbuch der pharmaceutischen Praxis, edited by B. Fischer and C. Hartwich, ed. 1, Berlin, Julius Springer, 1903 vol. 1, p. 1032.)

**Tests—**

\* German "digitalin" is  
in water and alcohol,  
to contain from about  
6 per cent of digitalins.  
Sulfuric acid contains  
digitalin; "German" an intense golden yellow coloration, changing to  
red and finally to a permanent reddish violet.

**DIGITALINE NATIVELLE.**—Digitaline Cristallisee (Nativelle)—A glucosidal substance derived from the dried leaves of *Digitalis purpurea*, first prepared by Nativelle (*J Pharm Chem* 9, 225, 1869). The empiric formula of digitaline Nativelle closely approximates  $C_{41}H_{64}O_{11}$ . It is standardized by the intravenous cat method of Hatcher and Brody so that 0.42 mg equals 1 cat unit, but the therapeutic dose is much less than that of digitalis in terms of cat units.

**Actions and Uses**—The action of digitaline Nativelle is like that of digitalis.

**Dosage**—The dose for the patient who has weeks by the oral mg of digitaline Nativene given in fractional doses. This is the therapeutic equivalent of from 13 to 16 Gm of digitalis. The total dose is given in fractions of from 0.25 to 0.5 mg, at intervals of from four to six hours. The total daily maintenance dose is from 0.1 to 0.2 mg. Patients may be digitalized by starting with total daily doses of 0.2 mg, such doses usually induce the full therapeutic effects in about one week. The great potency of digitaline Nativene requires a careful observance of the proper technique of its administration.

Poisoning with digitalis Nativelle requires no treatment except the utmost quiet in bed, with a sedative, such as pheno-barbital, if necessary to secure rest. The stomach should not be washed unless there is reason to believe that it contains some of the poison, but severe and repeated vomiting is a prominent symptom of poisoning with all digitalis bodies.

#### Tests and Standards—

Digitaline Nalavelle appears as thin colorless odorless elongated rectangular platelike crystals possessing a bitter taste. It is practically insoluble in water, ether and glycerin, soluble in acetone, chloroform, ethyl alcohol and pyridine. Digitaline Nalavelle may sinter at 230 C. and melts finally at from 253 to 263 C.

Digitaline Nativelle dissolves in cold, concentrated hydrochloric acid to form a colorless solution, but if this solution is heated on a water bath a green color should be obtained.

Dissolve a crystal of digitaline Nativelle in 2 cc. of glacial acetic acid containing a trace of ferric chloride and layer the solution on 2 cc. of concentrated sulfuric acid; a brown color should be produced at the zone of contact of the two liquids. This color gradually changes to green and finally to indigo blue; after half an hour the entire acetic acid layer will become blue.

#### E. FOUGERA AND CO., INC.

Tablets Digitaline Nativelle: 0.1 mg. and 0.2 mg.

Solution Digitaline Nativelle, 1:1,000: 10 cc. glass stoppered bottles. Each 1 cc. contains 1 mg. of digitaline Nativelle in a mixture of alcohol and glycerin

**DIGITAN.**—A purified extract of digitalis containing the active principles in the same proportions as they exist in the whole leaf. In digitan, 85 per cent of the inactive substances present in the ordinary extract have been removed and it is free from digitonin. Digitan is physiologically standardized according to the official U. S. P. XII procedure.

*Actions and Uses.*—The same as those of digitalis

*Dosage.*—The same as that of digitalis

*Preparation.*—

Digitan is obtained by removing objectionable constituents from an alcoholic extract of digitalis, neutralized with alkaline hydroxides, by the addition of ether, petroleum benzine or some other suitable precipitant, and reducing the purified liquid to a powder by evaporating with milk sugar.

*Tests.*—

Digitan is a greenish-yellow, odorless, bitter powder. The active constituents of digitan are insoluble in cold water and diluted acids, but are easily soluble in weak alkalis.

Digitan responds to the following identity test: If 0.1 Gm of digitan is underlaid with about 3 cc of glacial acetic acid which contains 1 per cent of a 5 per cent solution of ferric sulfate, there appears a red band (*presence of digitatin*) and above this another, at first bright green, later changing to dark green and finally blue (*presence of digitonin*)

The physiologic activity is determined by the official U. S. P. procedure.

#### MERCK & CO., INC.

Digitan (Powder).

Ampules Digitan (for Hypodermic Use): 1 cc. A sterilized solution of digitan, 0.1 Gm. per cubic centimeter.

Tablets Digitan: 0.1 Gm

Tincture Digitan: Each 1 cc contains digitan, 0.1 Gm

U. S. patent 943,578 (Dec. 4, 1909, expired). U. S. trademark 138,484

**DIGITOL**—Fat Free Tincture of Digitalis Mulford.—A biologically standardized fat free tincture of digitalis corresponding in drug strength to tincture of digitalis U. S. P. and containing 68 per cent alcohol.

**Actions and Uses**—The same as those of digitalis. Digitol was introduced at a time when the "fat" of digitalis was believed to cause gastric disturbances. At present the claim of superiority on this basis is not tenable. The only advantage of the detaching process is to make possible a nearly clear mixture of the product with water.

**Dosage**—From 0.3 to 1 cc.

#### **Preparation**—

Digitalis which has previously been subjected to percolation with petroleum benzene is extracted by percolation with hydroalcoholic menstruum in the usual way.

Digitol is a brownish green liquid having a characteristic and highly alcoholic odor and a bitter taste. Each cc. represents 0.6 g. of Digitalis U. S. P.

SHARP & DOHME, Inc.

#### **Digitol (Liquid)**

**GITALIN (AMORPHOUS)**—A glucosidal constituent of Digitalis purpurea Linné prepared according to the method of Kraft. It is standardized by the gravimetric method of Hatcher and Brody (*Am. J. Pharm.* 82:30, 1910) and its potency adjusted to an M. L. D. of 0.8 mg. per kilogram of body weight.

**Actions and Uses**—The same as those of digitalis.

**Dosage**—Until digitalis effects are usually obtained after a total dosage of 4 to 6.5 mg. or five to eight tablets. These effects may be obtained by the administration of two to three tablets per day for three or four days. The same precautions should be taken with gitalin as with any digitalis preparation or digitalis extract. Severe toxic symptoms such as tachycardia or irregularities during the course of digitalization, abnormality of the digestive tract, etc., are rare. After the desired clinical effects have been obtained the patient may be placed on a maintenance dose of 0.25 mg. to 0.4 mg. (one to three tablets) daily. The amount varies according to the individual requirements of the patient. In all cases gitalin should be given on an empty stomach and the dose should be gradually increased as the patient's condition improves. A full therapeutic effect has been observed with 0.8 mg. per kilogram of body weight daily, and a dosage of 0.2 mg. per kilogram of body weight is usually sufficient to maintain the desired effect. The following table shows the approximate maintenance dose for various weights of body.

#### **Dosage Table**

Weight of body in pounds. . . . . 120 150 180 200 220 250 300 350 400 450 500 600 700 800 900 1000  
Maintenance dose of gitalin (in mg.) . . . . . 0.25 0.31 0.37 0.40 0.45 0.50 0.60 0.70 0.80 0.90 1.00 1.20 1.40 1.60 1.80 2.00



with sodium sulfate. The resulting filtrate is agitated with chloroform and allowed to separate. From the chloroform extract the gitalin (amorphous) substance is precipitated by means of petroleum ether. The precipitate is subjected to further purification and finally dried in vacuo. The entire process of extraction and purification is conducted without the aid of heat.

### Tests.—

**Gitalin (amorphous)** is a white or slightly buff colored amorphous powder which is readily soluble in chloroform, ether, acetone and alcohol and is slowly soluble in 600 parts of cold water. It is insoluble in petroleum ether and carbon disulfide. Its aqueous solution is neutral to litmus and possesses an intensely bitter taste. It has no sharp melting point but undergoes some decomposition when heated to 110 C. and becomes fluid as the temperature is raised to 150 C. When its aqueous solution is boiled, gitalin (amorphous) is converted into anhydrogitalin, with a subsequent loss of about 30 per cent in potency.

Dissolve 10 mg. of gitalin (amorphous) in 3 cc of glacial acetic acid in a narrow test tube, and add to this one drop of 5 per cent ferric chloride solution. Underlay this solution with concentrated sulfuric acid; a brownish red zone appears at the point of contact. The upper acetic acid layer assumes a bluish green color, gradually changing to indigo blue. Repeat the test without the addition of ferric chloride; a brown zone appears at the point of contact, and the upper acetic acid layer remains green. Concentrated sulfuric acid containing 10 mg. of gitalin (amorphous) and a trace of ferric chloride produces a brown color, gradually changing to red and finally to violet. When an aqueous solution of gitalin (amorphous) is heated for one hour at 100 C., its potency is reduced 30 per cent. This "titer-drop" is a characteristic feature of gitalin (amorphous) and is due to the conversion of gitalin into anhydrogitalin. It does not occur with digitoxin.

### RARE CHEMICALS, INC.

**Tablets Gitalin (Amorphous):** 08 mg. Each tablet is scored into segments of 0.25 mg. for convenience in regulation of the daily maintenance dose.

### Related Digitalis Principles

**OUABAIN.**—*G Strophanthum*—"A glycoside occurring in *Acokanthera Ouabaio* Arnaud and obtained from the seeds of *Strophanthus gratus* (Wall. et Hook) Baillon (Fam. *Apocynaceae*)," U. S. P.

For description and standards see the U. S. Pharmacopeia under Ouabainum and Injectio Ouabaini.

**Actions and Uses.**—The pharmacologic action of ouabain is probably qualitatively identical with that of the official *strophanthus* or *strophanthin*, but ouabain is more active than the official *strophanthin* when injected intramuscularly or intravenously. This action develops more rapidly, the drug is more quickly excreted, and shows less tendency to cumulative action than does digitalis.

Ouabain is used only for injection in place of *strophanthus* or *strophanthin* as a substitute for digitalis.

**Dosage.**—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.



Dissolve about 0.5 Gm. of scillaren B, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20 C.: the specific rotatory power in alcohol  $[\alpha]_D^{20}$  falls between +35 and +41.

Ignite about 0.1 Gm. of scillaren B, accurately weighed; the residue does not exceed 0.1 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C.: the loss in weight does not exceed 2 per cent.

Transfer about 0.2 Gm. of scillaren-B, accurately weighed, previously dried over sulfuric acid in a partial vacuum, to a 250 cc. Erlenmeyer flask, dissolve in 5 cc. of water and add 20 cc. of a 5 per cent sulfuric acid; heat on a steam bath for six hours, cool, and collect the separated yellowish brown lumps on a Gooch crucible; wash free from acid with water, dry for twenty-four hours at 60 C., and weigh: the amount of aglucone found is not less than 50 per cent nor more than 57.5 per cent.

### SANDOZ CHEMICAL WORKS, INC.

**Ampul Solution Scillaren-B:** 0.5 mg. in 1 cc.

U. S. patent 1,516,552 (Nov. 25, 1924; expired) and 1,579,338 (April 6, 1926; expires 1943) U. S. trademark 173,046

**SCILLAREN.**—*Glucosidum e Scilla Totum.*—A mixture of the natural glycosides, scillaren-A and scillaren-B, occurring in fresh squill *Urginea maritima*, in the proportions in which they exist in the fresh crude drug; namely, about 2 parts of scillaren-A to 1 part of scillaren-B. Completely dried scillaren contains approximately 98 per cent of the active glycosides. Scillaren dried in a high vacuum at 78 C. for fifteen hours loses not more than 6 per cent of its weight.

**Actions and Uses.**—The cardiac action of scillaren is essentially similar to that of digitalis, but this action is apparently less persistent than that of digitalis.

**Dosage.**—1.6 mg. orally from three to four times daily until compensation is established or until minor toxic symptoms are induced. After compensation is established, 0.8 mg. may be administered from two to four times daily.

### Tests and Standards.

Scillaren occurs as a white or yellowish-white, odorless granular powder, possessing a very bitter taste, soluble in absolute ethyl alcohol 1 in 5, in methyl alcohol 1 in 5, sparingly soluble in water, 1 in 3,000, practically insoluble in chloroform, and in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of scillaren is levorotatory.

Dissolve about 0.001 Gm. of scillaren in 0.1 cc. of methyl alcohol, add 3 cc. of acetic anhydride, followed by the addition of 0.1 cc. of sulfuric acid, agitate and cool: a violet red color results, immediately turning to a bluish green (*this color reaction is due to the mixture of aglucones*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid solution and heat the mixture under a reflux condenser on a steam bath; after five minutes the aglucone, . . . . . for thirty minutes, . . . . . with water and . . . . . turning with decom . . . . . reaction character . . . . . heating the filtrate



water and dry at 105 C.; its melting point is not definite, occurring at about 220 C. and responding to the foregoing color reaction. The neutralized filtrate reduces alkaline cupric tartrate solution immediately.

Dissolve about 0.025 Gm. in 2 cc. of a mixture of 4 parts of ethyl alcohol (by volume) and 1 part of carbon dioxide free water; a clear colorless solution results, which remains clear on dilution with an equal volume of carbon dioxide free water (*aglucone*). Add to the foregoing solution 0.1 cc. of lead acetate solution; no immediate coloration or precipitation results (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc. of methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate solution and heat to boiling; the blue color persists for some time (*reducing free sugars*). Dissolve about 0.5 Gm. of scillaren-A, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20 C.; the specific rotatory power in alcohol  $[\alpha]_{20/D}$  falls between  $-72$  and  $-78$ .

Incinerate about 0.1 Gm. of scillaren-A, accurately weighed; the residue does not exceed 0.1 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C.; the loss in weight does not exceed 25 per cent.

Transfer about 0.2 Gm. of scillaren-A, accurately weighed, previously dried over sulfuric acid in a partial vacuum, to a 250 cc. Erlenmeyer flask, add 10 cc. of methyl alcohol and 10 cc. of tenth normal sulfuric acid solution, reflux on a steam bath for fifteen minutes, disconnect the condenser and boil on the steam bath until reduced to about a 10 cc. volume, cool and collect the crystals formed on a Gooch crucible, wash free from acid with water and dry to constant weight at 105 C.; the amount of aglucone found should not be less than 45 per cent, nor more than 55 per cent.

## SANDOZ CHEMICAL WORKS, INC.

**Tablets Scillaren:** 0.8 mg

**Solution Scillaren:** Each cubic centimeter represents 0.8 mg of scillaren.

U. S. patent No. 1,516,552 (Nov. 23, 1924; expired) and No. 1,579,338 (April 6, 1926; expires 1943). U. S. trademark 173,046.

**Dosage**—2 cc. (40 drops) three to four times daily; after compensation is established, 1 cc. (20 drops) two to four times daily. A dropping device is supplied with each package, designed to yield 20 drops per cubic centimeter.

**URGININ.**—A mixture of two water insoluble glycosides, urginin-A and urginin-B, derived from squill, in the proportions in which they exist in the drug; namely, about equal parts. The product is standardized so that the variation in the proportion of each glycoside is not more than plus or minus 2.5 per cent (from 50 per cent), i. e., 47.5 to 52.5 per cent. Urganin dried in a high vacuum at 50 C. for five hours loses not more than 2 per cent of its weight. Physiological standardization by the Hatcher-Brody cat method as modified by C. DeLind Van Wijngaarden, Arch. exper. Path. u. Pharm., 113:40, 59; 114:21, 1926, and by J. H. Burn, Methods of Biological Assay, Oxford University Press, 1928, demonstrates the lethal dose of urginin for cats to be 0.2 mg per Kg (one cat unit).

**Actions and Uses**—The cardiac action of urginin is essentially similar to that of digitalis

**Dosage**—Where digitalis has not been used within one week 3 mg daily in divided doses given at intervals of 6 hours, until the usual effects of the drug are observed, after which the maintenance dose of 0.5 to 10 mg may be given daily. In milder cardiac disorders, from 0.5 mg to 2 mg of urginin per day may be given

### Tests and Standards—

Urginin occurs as a pale yellow, granular powder possessing a slight characteristic odor and an extremely bitter taste, soluble in acetone, alcohol, ethyl acetate, glacial acetic acid dilute alkali carbonate and hydroxide solutions sparingly soluble in chloroform practically insoluble in water, carbon tetrachloride ether and purified petroleum benzene. A saturated aqueous solution is neutral to litmus. An alcoholic solution is levorotatory. Dissolve about 0.001 Gm of urginin in 2 cc of acetic anhydride followed by the addition of 0.1 cc. of sulfuric acid agitate and cool a rose color appears changing to violet then to green (*this color reaction is due to the mixture presumably of apigenins*). Dissolve about 0.2 Gm of urginin in 25 cc of ethyl alcohol add 1 cc of sulfuric acid and heat the mixture under a reflux condenser on a steam bath for six hours. The reamification

sugars)

Ignite about 0.1 Gm of urginin accurately weighed; the residue does not exceed 0.25 per cent. Dry about 0.2 Gm of urginin accurately weighed over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C; the loss in weight does not exceed 4 per cent. Dissolve about 0.5 Gm of urginin accurately weighed in 25 cc of 95 per cent ethyl alcohol, observe the angular rotation at 20 C the specific rotatory power  $[\alpha]_{20/D}$  falls between  $-18.0$  and  $-21.5$ . Transfer about 0.5 Gm of urginin, accurately weighed previously dried over sulfuric acid in a partial vacuum to a suitable Erlenmeyer flask dissolve in 7 cc of alcohol followed by the addition of 7 cc of a mixture of 1 cc of sulfuric acid and 25 cc of water connect with condenser and reflux on a steam bath for six hours disconnect the condenser neutralize the mixture with normal sodium hydroxide solution using phenolphthalein as an indicator add 0.1 cc of sulfuric acid remove the alcohol by heating on the steam bath until reduced to about a 10 cc volume add 10 cc of water mix thoroughly and evaporate to about 10 cc, cool and collect the separated crystalline and dark waxy resinous residue on a filter paper, wash the residue with water using three portions of 10 cc each, dissolve the residue in warm alcohol by passing it through the filter and collecting in a tared beaker, evaporate to a pulular consistency on the steam bath and dry for three hours at 90 C the amount of hydrolytic residue found is not less than 70 per cent nor more than 75 per cent

## LEDENLE LABORATORIES, INC.

## Urginin (Powder).

Coated Tablets Urginin: 1.0 mg.

Tablets Urginin: 1.0 mg.

U. S. patent 1,972,876 (Sept. 11, 1934; expires 1951). U. S. trade mark 324,695.

**STROPHANTHIN.**—"A glycoside or a mixture of glycosides obtained from *Strophanthus Kombe* Oliver (Fam. *Apocynaceae*).

"Strophanthin, when assayed as directed, shall possess a potency per mg. equivalent to 0.5 mg. of U. S. P. Ouabain Reference Standard." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Strophanthinum*.

## ELI LILLY AND COMPANY

Hypodermic Tablets Strophanthin: 0.6 mg.

## Organic Nitrates

The esters of nitric acid and the higher alcohols (glycerin, propanetriol, erythrite, butanetetrol, etc.) have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). This is generally attributed to the formation in the body of nitrites from them.

**ERYTHRITYL TETRANITRATE TABLETS.**—Erythrol Tetranitrate Tablets.—Tetranitrol Tablets—"Contain not less than 93 per cent and not more than 107 per cent of the labeled amount of erythrityl tetranitrate  $[C_4H_8(NO_2)_4]$ " U. S. P.

For description and standards see the U. S. Pharmacopeia under *Tabellae Erythritylis Tetramitris*.

**Actions and Uses.**—Erythrityl tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting, beginning in fifteen minutes and persisting for three or four hours.

It is said to be useful in angina pectoris and certain vascular diseases. It is reported as especially useful as a prophylactic in preventing anginal pain. Its use is sometimes attended with severe headache.

**Dosage**—From 30 mg. to 60 mg. every four to six hours.

## BURROUGHS WELLCOME &amp; CO., INC.

Tabloid Erythrityl Tetranitrate: 16 mg., 32 mg. and 65 mg.

MERCK & Co, INC

Tablets Erythrol Tetranitrate 52 mg and 16 mg

### Quinidine

**QUINIDINE** — *Quinidina* — An alkaloid  $C_{20}H_{24}O_2N_2 \cdot 2H_2O$  obtained from the bark of various species of *Cinchona*

Quinidine is obtained from cinchona bark as a by product in the manufacture of quinine, to which it is closely related being its stereoisomer

*Actions and Uses* — Quinidine like quinine is a protoplasmic poison. It affects protozoa more than bacteria but less powerfully than quinine. At one time it was used to some extent, as a substitute for quinine because it was then much the cheaper preparation. It has the antimalarial action of quinine and may be tolerated by some patients who have an idiosyncrasy to quinine.

Quinidine acts upon the heart in such a manner as to bring about cessation of fibrillation of the auricles in a certain proportion of instances. Quinidine and other cinchona alkaloids are the only drugs known to have this specific effect. The

fibrillation. This has been brought about in approximately 50 per cent of the reported cases in which the drug has been used. It is apparently most efficacious in the cases of fibrillation of short duration or of the paroxysmal type. It may also stop fibrillation of several years duration. It is least effective in cases of fibrillation with marked cardiac insufficiency. It is useful in slowing the rate in ventricular tachycardia following infarction of the myocardium. Quinidine is not without some unpleasant and even dangerous effects. Some patients appear much more susceptible to its intoxication than others. The untoward symptoms brought about by its use in these patients are nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. In most cases following the administration of the drug the pulse increases in rapidity before the normal rhythm is established. In some cases the effect of the drug is restricted to this alteration of rhythm. In a few instances such serious results as rapid idioventricular rhythms (ventricular tachycardia) have been initiated during the course of therapy. Toxic effects may appear after the establishment of a normal rhythm. Some cases have been reported in which sudden death occurred a short time after the drug had been stopped. The drug is rapidly eliminated and it apparently has no cumulative effect.



**Dosage.**—Quinidine is generally administered as quinidine sulfate. Commonly 0.2 Gm of quinidine sulfate is given as a preliminary dose and is repeated after two hours to determine the patient's susceptibility to the drug. If there are no symptoms following this preliminary dose, therapeutic administration is begun on the following day when from 0.2 Gm to 0.4 Gm. is given from three to five times daily, for one to three days. As a rule, if the establishment of the normal rhythm can be effected, the change occurs after from one to three days' treatment. The maximum dose per day advised by most authors is from 1 to 2 Gm. In ventricular tachycardia following cardiac infarction, larger doses are sometimes required and are well tolerated. If toxic symptoms occur, the administration of the drug should be discontinued. Intravenous administration is dangerous and is not recommended.

### Tests and Standards—

Quinidine occurs in white crystals or as an amorphous, white powder; odorless, taste, intensely bitter and persistent; efflorescent in dry air. Quinidine is very slightly soluble in water; soluble in alcohol and ether; freely soluble in chloroform; very slightly soluble in petroleum benzene.

The saturated aqueous solution of quinidine is alkaline to litmus and its alcoholic solution is dextrorotatory. A solution of quinidine in diluted sulfuric acid (1 in 1,000) shows a strong blue fluorescence.

Quinidine loses its water of hydration at 100 C. The dried alkaloid melts at about 168 C.

Add a few drops of bromine water to 10 cc. of an aqueous solution of quinidine (1 in 1,000), prepared with just sufficient diluted sulfuric acid to produce complete solution, and follow with ammonia water in slight excess. The liquid acquires an emerald green color.

Dissolve about 0.1 Gm of quinidine in 15 cc. of hot water containing a few drops of diluted sulfuric acid; cool the solution; add 1 cc. of silver nitrate solution and stir the mixture with a glass rod. A white, crystalline precipitate forms after a short interval (*distinction from many other alkaloids*).

Dissolve about 0.1 Gm. of quinidine in 10 cc. of warm water containing a slight excess of diluted hydrochloric acid; add an excess of potassium iodide solution and agitate, an orange yellow, crystalline precipitate forms after an interval (*distinction from quinine*).

Dissolve 0.5 Gm. of quinidine in 15 cc. of boiling distilled water, with just enough sulfuric acid to form a solution neutral to litmus paper, and add 5 cc. of potassium iodide solution. Agitate the mixture gently; cool it to 15 C., and keep it at this temperature for one hour, with occasional stirring: a white precipitate is formed (*distinction from quinine*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate: not more than a slight turbidity results (*limit of other cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral after the addition of the potassium iodide solution; if slightly acid, very dilute ammonia water must be added, drop by drop, with constant stirring until exact neutrality to litmus is attained.

A solution of about 0.1 Gm of quinidine in 5 cc. of sulfuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 1 Gm. of quinidine, accurately weighed: the ash does not exceed 0.1 per cent.

Dry about 1 Gm of quinidine, accurately weighed, to constant weight at 100 C.: the loss does not exceed 11 per cent.

### MALLINCKRODT CHEMICAL WORKS

Quinidine (Powder): bulk.

MERCK & Co, INC

Quinidine (*Powder*) bulk

**QUINIDINE SULFATE**—"A sulfate of an alkaloid obtained from the bark of the stem or of the root of various species of cinchona and their hybrids (Fam *Rubiaceae*)' U S P

For description and standards see the U S Pharmacopeia under Quinidinae Sulfas and Tabellae Quinidinae Sulfatis

*Actions and Uses*—See preceding article, Quinine

*Dosage*—See preceding article, Quinine Quinidine sulfate may be administered in the form of cachets, capsules, pills or tablets

ABBOTT LABORATORIES

Capsules Quinidine Sulfate 0.2 Gm

DAVIES, ROSE & COMPANY, LTD

Tablets Quinidine Sulfate. 0.2 Gm

MALLINCKRODT CHEMICAL WORKS

Quinidine Sulfate (*Powder*) bulk

MERCK & Co, INC

Quinidine Sulfate (*Powder*)• bulk

### Sclerosing Agents

Solutions of ethyl alcohol, dextrose invert sugar, iodides, iron salts, mercuric chloride, phenol quinine and urea hydrochloride salicylates, sodium chloride sodium citrate, sodium morrhuate and others have been employed as sclerosing agents mainly for the obliteration of varicose veins. Some of the compounds employed for this purpose are combined with local anesthetic agents or possess anesthetic properties themselves. Solutions of dextrose or invert sugar and fatty acid preparations such as

with local anesthetics and quinine hydrochloride or quinine chloride (13 per cent) with urethane (6.5 per cent) for use as sclerosing agents in the obliteration of varicose veins only

**SOLUTION OF DEXTROSE 50% (w/v)**—See preceding article for actions and uses. For accepted brands see under Parenteral Solutions—Dextrose

**SOLUTION OF INVERT SUGAR.**—A solution of a mixture of dextrose and levulose obtained by the inversion of sucrose.

*Actions and Uses.*—Solution of invert sugar is used in the injection treatment of varicose veins. It is claimed that the use of sugar solutions such as solutions of dextrose or of invert sugar have the advantage over solutions of sodium chloride, sodium salicylate or mercuric chloride in that they do not cause severe cramps or sloughing if accidentally injected outside the vein.

*Dosage.*—Depending on the size of the vein, from 5 to 20 cc. of solution is injected. For young patients whose veins react to solutions of less concentration, solutions containing from 50 to 60 Gm. of invert sugar in 100 cc. are used; for older patients and varicosities of long standing, a solution containing 75 Gm. of invert sugar in 100 cc. is used.

#### *Tests and Standards.*—

Solution of invert sugar is prepared by inverting cane sugar with tartaric acid and adjusting to a *pn* of 6.8 with sodium hydroxide.

Solution of invert sugar is a clear, pale amber, sweet, watery solution

A 10 cc. portion requires less than 2 cc. of tenth-normal sodium hydroxide to neutralize the acid, phenolphthalein being used as an indicator. No sediment separates from the solution in ampules on prolonged standing (*insoluble salts, ultramarine or prussian blue*). A 10 per cent solution is not affected by the addition of an equal volume of hydrogen sulfide solution (*heavy metals*). Ten cc. portions of a 10 per cent solution remain clear for at least one minute after the addition of 1 cc. of silver nitrate solution (*chloride*) or of ammonium oxalate solution (*calcium*). A portion equivalent to 5 Gm. of invert sugar shows no more sulfate than corresponds to 0.3 cc. of fiftieth normal sulfuric acid according to the U. S. P. X test. A solution equivalent to 5 Gm. of invert sugar evaporated to dryness and ashed yields a residue weighing not more than 0.004 Gm. A solution equivalent to 5 Gm. of invert sugar yields not more ammonia than is equivalent to 0.5 cc. of hundredth-normal hydrochloric acid. A solution containing 16 per cent of invert sugar calculated from its copper reducing power, when examined by means of the polariscope has a specific rotation of  $[\alpha]_D^{25}$  between  $-16$  and  $-18.5$ .

Dilute exactly 10 cc. of the original to exactly 500 cc.; transfer 10 cc. of this solution to a 250 cc. beaker and assay for invert sugar according to paragraphs 37 and 38 on page 479 of the 1936 edition of the A. O. A. C. Manual; the amount of invert sugar is within 5 per cent of the amount claimed. Transfer 50 cc. of the prepared solution to a 100 cc. standard flask; invert according to paragraph 23 C, page 473 of the A. O. A. C. Manual and assay for sucrose according to paragraph 28, page 476 of the A. O. A. C. Manual; the weight of sucrose is not greater than 4 per cent of the weight of invert sugar found.

**SODIUM MORRHUATE.**—A mixture of the sodium salts of the saturated and unsaturated fatty acids occurring in cod liver oil.

*Actions and Uses.*—The action of sodium morrhuate is that of a sclerosing agent. It is employed in solution with addition of a local anesthetic for the obliteration of varicose veins. Solutions in concentrations of more than 5 per cent are not

recommended, and the possibility of sensitization or idiosyncrasy to sodium morrhuate should be kept in mind to avoid reactions which have been reported in susceptible individuals

*Dosage*—One half to 1 cc. of a 5 per cent solution is a relatively safe preliminary test dose and its effects should be studied for 24 hours before proceeding with further injections. An average of 1 cc. is the amount injected at any one site and should not exceed 2 cc. The number of injections made in one day varies with the patient and should not comprise a total amount of more than 5 cc. To guard against the development of sensitivity it is recommended that the interval of time between the first two injections be not more than five days

### *Tests and Standards—*

Sodium morrhuate is a pale yellowish granular powder, possessing a slight fishy odor. It is soluble in water.

Incinerate about 1 Gm. of sodium morrhuate; the residue responds to test for sodium carbonate. Dissolve about 0.01 Gm. of sodium morrhuate in 10 cc. of water, add 1 cc. of chloroform followed by one drop of sulfuric acid and shake; a violet red color results gradually changing to a reddish brown.

Dry about 1 Gm. of sodium morrhuate, accurately weighed at 100 C. for six hours; the loss does not exceed 2 per cent. Weigh accurately

to the dried substance

Transfer about 25 Gm. of sodium morrhuate to a suitable Squibb separatory funnel; add 350 cc. of water and sufficient diluted sulfuric acid to precipitate the fatty acids and extract with 3 portions of ether, using 150 cc., 100 cc., and 50 cc., respectively. The combined ethereal solutions, evaporated to an oily liquid on the steam bath, conform to the following requirements:

Morrhucic acid, a component of sodium morrhuate, responds to the following tests for identity, purity and assay. Morrhucic acid occurs as a light amber oily liquid possessing a slight fishy odor and taste.

In a 500 cc. flask add 10 cc. of chloroform followed by the addition of 25 cc. of iodochloride test solution (Wijs modification), accurately measured stopper the flask and allow to stand for thirty minutes in a cool place protected from light. To the mixture add 20 cc. of a 15 per cent solution of potassium iodide mix thoroughly, add 200 cc. of water previously boiled and cooled and titrate the excess of iodine with tenth normal sodium thiosulfate solution, using starch paste as an indicator. While the foregoing is being performed make a control test by using exactly the same quantities of reagents and titrate the free iodine with tenth normal sodium thiosulfate solution; the amount of tenth normal sodium thiosulfate solution consumed corresponds to an iodine value of not less than 145 and not more than 185.

Dissolve about 1 Gm. of morrhucic acid, accurately weighed in 50 cc. of alcohol and titrate with tenth normal potassium hydroxide solution using phenolphthalein as an indicator; the amount of tenth normal potassium hydroxide solution consumed corresponds to an acid value which should not be less than 183 and not more than 198.

Digest about 5 Gm. of morrhue acid under a reflux condenser with a solution of about 2 Gm. of potassium hydroxide in 40 cc. of alcohol for an hour or until saponified. Evaporate most of the alcohol, dissolve the residue in 50 cc. of hot water; transfer the solution to a separatory funnel, rinsing the flask with 25 cc. to 50 cc. of hot water; cool; extract with ether, using 2 portions of 50 cc. each, adding if necessary about 5 cc. of alcohol to facilitate the separation of two liquids; wash the combined ether extraction with small portions of water until not reddened by phenolphthalein; transfer the ethereal solution to a tared beaker; evaporate the ether on a water bath; dry the residue at a temperature not exceeding 100 C., and weigh; the unsaponifiable matter does not exceed 15 per cent.

#### **GEORGE A. BREON & COMPANY, INC.**

**Solution of Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 5 cc. vials. Each cubic centimeter contains sodium morrhuate 0.05 Gm. and benzyl alcohol 0.02 Gm. in aqueous solution.

#### **BURNOUGH'S WILLCOCKE & CO., INC.**

**Hypoloid Sodium Morrhuate Injection 5%:** 2 cc. Each cubic centimeter contains sodium morrhuate 0.05 Gm. and 0.5 per cent of phenol as a preservative.

**Hypoloid Sodium Morrhuate Injection 5%:** 25 cc. rubber capped bottle. Each cubic centimeter contains sodium morrhuate 0.05 Gm. and 0.5 per cent of phenol as a preservative.

#### **CHEPLIN BIOLOGICAL LABORATORIES, INC.**

**Ampoule Solution Sodium Morrhuate 5% W/V with Tricresol 0.3%:** 2 cc. and 5 cc. ampoules and 30 cc. vials. Each cubic centimeter contains sodium morrhuate 0.05 Gm.; tricresol 0.003 cc. as a preservative, double distilled water q. s.

#### **ENDO PRODUCTS, INC.**

**Ampoules Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 2 cc. and 5 cc. Each cubic centimeter contains sodium morrhuate 0.05 Gm. and benzyl alcohol 0.02 Gm. in aqueous solution.

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 25 cc. bottle. Each cubic centimeter contains sodium morrhuate 0.05 Gm. and benzyl alcohol 0.02 Gm. in aqueous solution.

#### **THE LAKESIDE LABORATORIES, INC.**

**Ampules Solution Sodium Morrhuate 5% and Benzyl Alcohol 2%:** 2 cc. and 5 cc. Each cubic centimeter contains 0.05 Gm. sodium morrhuate and 0.02 Gm. benzyl alcohol in aqueous solution.

**Sodium Solution Morrhuate 5% and Benzyl Alcohol 2%:** 5 cc. and 30 cc. vials. Each cubic centimeter contains 0.05 Gm. of sodium morrhuate and 0.02 Gm. of benzyl alcohol in aqueous solution.

## THE NATIONAL DRUG CO

**Ampuls Solution Sodium Morrhuate with Quinine** 5 cc Each cubic centimeter contains sodium morrhuate 0.05 Gm, quinine alkaloid 0.02 Gm, and benzyl alcohol 0.02 Gm in aqueous solution U. S. patent 2,037,196 (April 14, 1936 expires 1953) and 2,046,116 (June 30, 1936, expires 1953)

**Ampul-Vials Solution Sodium Morrhuate with Quinine** 25 cc Each cubic centimeter contains sodium morrhuate 0.05 Gm, quinine alkaloid 0.02 Gm, and benzyl alcohol 0.02 Gm in aqueous solution

**Ampuls Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%** 5 cc Each cubic centimeter contains 0.05 Gm sodium morrhuate and 0.02 Gm benzyl alcohol in aqueous solution

**Ampul-Vials Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%** 25 cc Each cubic centimeter contains 0.05 Gm sodium morrhuate and 0.02 Gm benzyl alcohol in aqueous solution

## G. D. SEARLE &amp; CO

**Ampul Solution Sodium Morrhuate 5% with Benzyl Alcohol** 5 cc and 60 cc. (serum type ampuls) Each cubic centimeter contains 0.05 Gm sodium morrhuate and benzyl alcohol 0.02 Gm in aqueous solution

## ULMER PHARMACAL COMPANY

**Sodium Morrhuate 5%, Solution with Benzyl Alcohol 3%** 5 cc and 20 cc vials Each cubic centimeter contains sodium morrhuate 0.05 Gm, benzyl alcohol 0.03 Gm, and phenol 0.005 Gm, in aqueous solution

## THE UPJOHN COMPANY

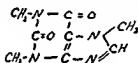
**Ampoule Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%** 2 cc Each cubic centimeter contains sodium morrhuate 0.05 Gm and benzyl alcohol 0.02 Gm in aqueous solution

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%** 30 cc vials Each cubic centimeter contains sodium morrhuate 0.05 Gm and benzyl alcohol 0.02 Gm in aqueous solution

## CHAPTER VIII

### CENTRAL NERVOUS SYSTEM STIMULANTS

**CAFFEINE AND SODIUM BENZOATE.**—"A mixture of caffeine and sodium benzoate, containing, when dried to constant weight at 80° C., not less than 47 per cent and not more than 50 per cent of anhydrous caffeine ( $C_8H_{10}N_4O_2$ ): and not less than 50 per cent and not more than 53 per cent of sodium benzoate ( $NaC_6H_5O_2$ )."  
U. S. P.



For description and standards see the U. S. Pharmacopeia under *Caffeina et Sodii Benzoas* and *Injectio Caffeinae et Sodii Benzoatis*.

**CARBON DIOXIDE.**—Carbonic Acid Gas.—"Contains not less than 99 per cent by volume of  $CO_2$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Carbonei Dioxidum*

*Actions and Uses.*—Carbon dioxide is the natural stimulant to respiration. It is frequently added to oxygen in varying proportions for supplying artificial respiration, and as a stimulant to the respiratory center. The proportions must be regulated carefully. A great excess of carbon dioxide causes death by asphyxia

**OXYGEN.**—"Oxygen contains not less than 99 per cent by volume of  $O_2$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Oxygenium*.

*Caution:* The usual precautions concerning use of oxygen apparatus must be followed. Special precaution must be observed against use of oil on valves

*Actions and Uses.*—Oxygen is administered for the purpose of relieving difficult respiration in cases of mechanical hindrance to the ingress of air to the lungs and in the treatment of carbon monoxide poisoning. It is also mixed with nitrogen monoxide when this gas is used as an anesthetic. Oxygen containing from 5 to 7 per cent of carbon dioxide is useful for resuscitation.

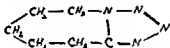
**OXYGEN-CARBON DIOXIDE MIXTURE**—A mixture in various proportions of carbon dioxide and oxygen.

For description and standards see the U. S. Pharmacopeia under Carbonic Dioxidum and Oxygenium respectively.

*Caution* The usual precautions concerning use of oxygen apparatus must be followed. Special precaution must be observed against use of oil on valves.

*Actions and Uses*—Oxygen carbon dioxide mixture in varying proportions for supplying artificial respiration and as a stimulant to the respiratory center.

**METRAZOL**—Pentamethylenetetrazol—



*Actions and Uses*—The action of metrazol resembles that of camphor, but it is claimed to be more dependable, mainly on account of its greater solubility in water. Its action following injection intravenously or subcutaneously is induced promptly. Metrazol stimulates the vasomotor and respiratory centers in experiments on normal animals, but an experienced worker in this field found it a very uncertain respiratory stimulant in conditions of depressed respiration in animals, in which carbon dioxide, epinephrine and ephedrine were markedly effective, that as a circulatory stimulant it usually caused a rise of blood pressure only in convulsive doses, that it did make irregularly beating hearts beat more regularly, but only at expense of depression of rate and amplitude. The use of metrazol is reported as a respiratory agent and reported as a shock agent.

Metrazol has come into extensive use in the treatment of mental disorders in doses which induce convulsions. Reports have appeared of minor fractures of the vertebrae, without paralysis, induced by these convulsions, hence this convulsive treatment should be instituted only by psychiatrists or in an institution where the necessary care can be given.

*Dosage*—Intramuscularly, subcutaneously, or intravenously from 0.1 to 0.3 Gm. repeated as required, orally, from 0.1 to 0.3 Gm. several times daily.



*Tests and Standards.*—

Metrazol occurs as biaxial, optically negative, white crystals that are freely soluble in water. It melts at 57-58 C.

To a 10 per cent aqueous solution of metrazol add a saturated solution of mercuric chloride; a white solid precipitate results, which may be recrystallized from hot water or alcohol to yield crystals melting at 177-178 C. and leaving not more than 0.1 per cent of ash on incineration.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a wide mouth weighing bottle; allow to stand over calcium chloride; the loss in weight is not more than 0.1 per cent.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a platinum dish and incinerate; the ash is not weighable.

Determine nitrogen by the Dumas method as described in Clarke's Handbook of Organic Analysis, ed. 2, New York, Longmans, Green & Co., 1916, p. 199; the nitrogen is not less than 40.4 nor more than 40.9 per cent.

**BILHUBER-KNOLL CORP.**

**Ampules Solution Metrazol:** 1 cc and 3 cc. Each 1 cc contains 0.1 Gm of metrazol in aqueous solution with 0.1 per cent sodium phosphate.

**Metrazol Oral Solution, 10 per Cent:** An aqueous solution containing metrazol, 0.1 Gm per 1 cc.

**Metrazol Sterile Aqueous Solution, 10 per Cent:** A sterile solution containing metrazol 0.1 Gm. per cubic centimeter, for parenteral administration.

**Tablets Metrazol:** 0.1 Gm.

U S patent 1,599,493 (Sept. 14, 1926; expires 1943) U. S. trade mark 249,687.

..... of pyridine-3( $\beta$ )carbox-  
acid diethylamide.—The  
N-diethyl nicotinamide —

*Actions and Uses.*—Experiments involving several species of animals indicate that the action of nikethamide is mainly on the central nervous system. In animals the drug appears to stimulate medullary centers, giving rise to an increased rate and depth of respiration and to peripheral vasoconstriction. Possibly the vasoconstriction may be in part due to a peripheral action of the drug. In animals its administration usually results in some increase in blood pressure, but this may be preceded by a temporary and sudden lowering of the pressure. Claims have been made for the use of nikethamide as an agent to raise blood pressure in human beings, but the results are not consistent; it has been suggested that any rise in blood pressure may be secondary to improved respiration and to stimulation of the reflex centers. Small doses in experimental animals exert no action on the coronary vessels, but larger doses may increase the coronary flow. However, clinical evidence for the use of nikethamide to promote increased coronary blood flow is not conclusive.

Nikethamide has been used clinically as a cardiac stimulant, but the majority of published reports do not reveal it to be  
 liac effect does  
 Most experi  
 sistent increase  
 ical effect in  
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nary thrombosis or coronary sclerosis) and angina pectoris. The analeptic action of nikethamide suggests its usefulness in combating acute respiratory depression from anesthetics, alcoholic intoxication and hypnotics. However, it is not clear that nikethamide is superior in this respect to other available drugs, especially in cases of barbiturate poisoning. Because of its action on peripheral vessels, nikethamide is contraindicated in cases of acute circulatory failure, such as occurs in surgical procedures or in pneumonia. It is also contraindicated in pulmonary embolism and in pulmonary venous thrombosis.

**Dosage.**—Nikethamide is available as an aqueous solution 25 per cent W/V, for oral and for subcutaneous, intramuscular or intravenous administration. When given orally, it should be expected from oral administration that the drug will be absorbed. It is true also for subcutaneous administration. When given intravenously, it should preferably be given intravenously. When given intravenously, administration is rapidly inactivated; the dose depends on the rate of injection. When doses larger than 3 cc are given, the administration should be slow and the general reaction of the patient should be watched. It should be remembered that large or toxic doses produce convulsions and may cause death from respiratory failure. The dose may be repeated at intervals according to the needs of the patient.

#### *Tests and Standards.*—

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 1 522  
 more  
 (W/V  
 water  
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acidify with dilute hydrochloric acid to a pH of 3.6 (slightly acid to congo red); collect the fine, white precipitate on a filter, wash with water and recrystallize from 5 cc. of water; collect on a filter and dry at 100 C.; the nicotinic acid obtained melts at 235-238 C.

Heat a few drops of nikethamide with 1 Gm. of sodium carbonate: a strong odor of pyridine results.

Dissolve 10 Gm. of nikethamide in 90 cc. of water: the solution is clear, nearly colorless and free from the odor of pyridine; it yields only a faint color of diethylamine. The solution will respond to the following

cautiously overlay 5 cc. of ferrous ammonium sulfate solution; no brown color appears at the interface (*nitrate*). Add 5 drops of dilute sulfuric acid to 5 cc. of the solution; extract twice in a separatory funnel with 20 cc. portions of a mixture of 3 parts of chloroform and 1 part of isopropyl alcohol; combine the extracts, filter, evaporate to dryness on a steam bath and dissolve the dry residue in 10 cc. of boiling water. When the solution is cool, add 0.1 cc. of tenth normal sodium hydroxide and 1 drop of phenolphthalein indicator; the solution turns red (*nicotinic acid*).

Warm 10 Gm. of nikethamide for one hour with 3 cc. of dilute hydrochloric acid and 6 cc. of water, cool and add 5 cc. of sodium hydroxide solution; the solution yields no distinct yellow color (*foreign organic impurities*).

A solution made by dissolving 1 Gm. of nikethamide in 5 cc. of car-

bon, add 5 cc. of water, transfer to a 100 cc. distilling apparatus, add 5 cc. of sodium hydroxide solution (1:1) and distill into a flask containing 10 cc. of 2 per cent boric acid solution colored with methyl red solution (1 drop in each 20 cc.). Titrate the solution with fiftieth normal sulfuric acid to a pink color, matched against a prepared blank. Each cubic centimeter of fiftieth normal sulfuric acid is equivalent to 3.565 mg. of nikethamide. The amount of nikethamide found should be not less than 99 per cent nor more than 100.5 per cent.

#### ABBOTT LABORATORIES

Sterile Ampoules Nikethamide 25% W/V: 1.5 cc. and 5 cc.

#### GEORGE A. BREON & COMPANY, INC.

Ampuls Solution Nikethamide 25% W/V: 2 cc.

Solution Nikethamide 25% W/V: 3 ounce, 15 cc., 88.7 cc. and 480 cc. bottles for oral use

#### BUFFINGTON'S, INC.

Ampuloids Sterile Solution Nikethamide 25% W/V: 2 cc. and 5 cc.

## DRUG PRODUCTS CO INC

Ampuls Solution of Nikethamide 25% W/V 1.5 cc

Solution of Nikethamide 25% W/V 30 cc vials Chlorobutanol 0.5 per cent added as a preservative

## ENDO PRODUCTS INC

Ampuls Solution Nikethamide 25% W/V 1½ and 5 cc

Solution Nikethamide 25% W/V 15 cc vials for oral administration

## FINT EATON &amp; COMPANY

Ampuls Solution Nikethamide 25% W/V 2 cc and 5 cc

## THE LAKESIDE LABORATORIES, INC

Ampul Solution of Nikethamide 25% W/V 15 cc  
0.5 per cent chlorobutanol added as a preservative

Ampul Solution of Nikethamide 25% W/V 2 cc and 5 cc

Solution of Nikethamide 25% W/V 15 cc vials with dropper for oral use

Solution of Nikethamide, 25% W/V 15 cc vial for injection with 0.5% chlorobutanol

## LEDERLE LABORATORIES INC

Ampul Solution Nikethamide 25% W/V 15 cc and 5 cc

## SMITH DORSEY CO

Ampoules Solution Nikethamide 25% W/V 15 cc and 5 cc

## THE UPJOHN COMPANY

Ampuls Solution Nikethamide 25% W/V 15 cc and 10 cc

Solution Nikethamide 25% W/V 88.7 cc bottle

## CHAPTER IX

### CHOLERETICS

#### Bile Salts and Related Compounds

The bile of man and of several animals contains the sodium salts of several conjugated oxycholanic acids in varying proportions. In ox and human biles glycocholic acid,  $C_{26}H_{46}O_6N$ , and taurocholic acid,  $C_{26}H_{46}O_7NS$ , are prominent constituents. Fresh ox bile is said to contain about 3 per cent each of sodium glycocholate and sodium taurocholate.

*Actions and Uses.*—The bile salts constitute the main active principles of bile, and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation, they cause severe nervous and cardiac depression, not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing the efficiency of the resinous hydragogue cathartics, and a prominent role in the digestion and absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile.

They have been used with doubtful rationale in obstructive jaundice; their use is more reasonable in nutritional disturbances accompanying biliary fistula. There is evidence to indicate that bile salts are useful to promote the intestinal absorption of food fats and fat soluble vitamins when failure to absorb these substances is due to lack of bile in the intestine.

The sodium glycocholate and taurocholate may be separated in the following manner. Dry ox bile is treated with absolute alcohol and the tincture precipitated by ether in excess. Both salts are deposited and the glycocholate crystallizes on standing, the taurocholate remaining in amorphous form, resembling oil or resinous matter. If the deposit is dissolved in water, solution of lead acetate will throw down a lead glycocholate, while the addition of lead subacetate to the remainder will precipitate the taurocholate.

*Tests.* All the bile acids respond to Pettenkoffer's test. A small portion of the salt is dissolved in a little concentrated sulfuric acid in a small porcelain dish and warmed, care being taken that the temperature does not rise higher than from 60 to 70 C. A 10 per cent solution of cane sugar is then added drop by drop while the liquid is stirred with a glass rod. If compounds of cholic acid are present a beautiful red color will appear, which does not disappear at room temperature, but usually in the course of a day becomes bluish violet. The red liquid shows in the spectrum two absorption bands, one at F and the other between D and E, nearer to E. Care must be taken not to heat too much or to add too much sugar. The sulfuric acid must be free from sulfurous acid and the lower oxides of nitrogen. As albumin, oleic acid, amyl alcohol, morphine, etc., may give a similar reaction, spectroscopic examination should not be omitted in doubtful cases (Hammarsten, *Lehrbuch der physiologischen Chemie*, ed. 6, p. 312). *Furfural Test (Mylus):* The substance is dissolved in alcohol and for every cubic centimeter of the alcoholic solution, 1 drop of a 1 in 1000 furfural solution and 1 cc of concentrated sulfuric acid are added and the mixture cooled, if necessary, so that the temperature may not rise too high. A blue color results.

**BILE SALTS**—A preparation obtained from fresh ox bile, consisting essentially of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile

*Actions and Uses*—See preceding general article Bile Salts and Related Compounds

*Dosage*—From 0.03 to 0.2 Gm

FAIRCHILD BROS AND FOSTER

Bile Salts: bulk

Capsules Bile Salts 0.2 Gm

• • • • • 1

*Actions and Uses*—See preceding general article Bile Salts and Related Compounds

*Preparation*—

Glycotauro is prepared by evaporating ox bile in the presence of animal charcoal extracting the residue with purified methyl alcohol filtering evaporating the filtrate and mixing the residue with glycerin

Glycotauro is a soft semisolid mass of light brown color bilelike odor and slightly bitter taste It is easily soluble in water and alcohol Its specific gravity is about 1.22

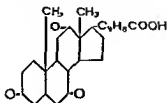
HANSON, WESTCOTT & DUNNING INC

Capsules Glycotauro (half size) 39 mg

Capsules Glycotauro 85 mg

Enteric Coated Tablets Glycotauro 78 mg, coated with salol

**DEHYDROCHOLIC ACID**—An oxidation product of cholic acid derived from natural bile acids



*Actions and*  
to increase the  
does not stim  
cholagogue),  
(choleretic action) is uncertain The production of hydrochol  
eresis may be of value to encourage drainage of the bile ducts  
by removal of mucus inspissated bile and debris and to dis

courage the ascent of infection in these structures in cholecystitis, noncalculous cholangitis and other conditions involving biliary stasis not due to complete mechanical obstruction. It should be kept in mind that a copious flow of bile can accomplish a flushing of the ducts but not, per se, of the gallbladder: the use of dehydrocholic acid in cholecystitis, with or without cholelithiasis, would not therefore be rational in cases where the gallbladder does not fill, except in the presence of stasis of the biliary ducts. In the presence of a decreased output of bile, where the gallbladder fills, hydrocholeresis may indirectly encourage drainage of this viscus if this is induced by the concomitant use of cholagogues. Flushing of the ducts appears less certain in the unoperated patient but may be encouraged by hydrocholeresis in conjunction with an antispasmodic in the presence of spasm of the sphincter of Oddi (spasm of this structure is less readily produced if the liver is secreting freely). Dehydrocholic acid may be employed similarly to encourage maintenance of T-tube surgical drainage of an infected common duct and as an aid in the removal of small stones or foreign material overlooked at operation. It is proposed for the purpose of outlining the bile ducts at operation and of accelerating the appearance of the gallbladder shadow and hastening removal of residual tetraiodophenolphthalein from the biliary tract in cholecystography.

Experimental evidence indicates that dehydrocholic acid does not significantly affect the rate of clearance of jaundice following relief of biliary obstruction and confirms the pharmacologic observation that bile salts do not affect the excretion of bile pigments. A few clinical studies favor the use of the drug in the treatment of arsenical and other forms of toxic hepatitis and of hepatic dysfunction, and as a diuretic—alone or in combination with the mercurials—in the treatment of ascites due to hepatic congestion in cardiac decompensation, cirrhosis or some other form of liver damage, but these have been too poorly controlled to warrant further recognition of such uses until more unequivocal evidence is available.

Dehydrocholic acid is contraindicated in complete mechanical biliary obstruction because the production of hydrocholeresis in this condition is irrational if not actually harmful. Its use in the presence of severe hepatitis may also be questioned on the ground that this condition may be aggravated or may reduce the hydrocholeretic effect, although more evidence is needed on these points before hepatitis can be regarded as a contraindication to the use of the drug.

*Dosage.*—From 0.25 to 0.5 Gm. two to three times daily after meals for a period of four to six weeks.

#### *Tests and Standards.*—

Dehydrocholic acid occurs as a fine, colorless, crystalline powder with a bitter taste; sparingly soluble in alcohol and glacial acetic acid. It melts at 233-235 C.

Boil about 1 Gm of dehydrocholic acid with 100 cc of water for two minutes, no odor develops, cool and filter. Separate portions of 10 cc each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*), no turbidity with 1 cc. of diluted nitric acid and 1 cc of barium nitrate solution (*sulfate*), no turbidity with 1 cc of diluted sulfuric acid (*soluble barium compounds*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*)

Dry about 1 Gm. of salt in a vacuum oven at 100°C. for 24 hours.

Loss on drying: 1.5% (maximum).  
 Residue on ignition: 0.5% (maximum).  
 Assay: 98.5% (minimum).

Not more than 101.5 per cent

GEORGE A BREON & COMPANY, INC

Tablets Dehydrocholic Acid: 0.25 Gm.

BURNOUGH'S WELLCOME & Co, INC.

Tabloid Dehydrocholic Acid: 0.243 Gm

THE LAKESIDE LABORATORIES, INC

Tablets Dehydrocholic Acid: 0.25 Gm

RIEDEL-DE HAEN, INC.

Decholin (*Powder*): bulk Dehydrocholic acid

Tablets Decholin: 3¼ grains

U S trademark 315,067

SMITH-DORSEY CO

Tablets Dehydrocholic Acid: 0.25 Gm

**SODIUM DEHYDROCHOLATE**—The sodium salt of dehydrocholic acid

*Actions and Uses*—The actions and uses of sodium dehydrocholate are the same as those of dehydrocholic acid

Calc. — 1 Gm. of salt contains 0.25 Gm. of dehydrocholic acid.

*Dosage* — Sodium dehydrocholate is administered intravenously. One injection is given on each of three successive days. According to the urgency of the case, the first dose consists of from 5 to 10 cc of the 20 per cent solution, the second and third, of 10 cc.

For determination of the arm to tongue circulation time, 3 to 5 cc. are rapidly injected (2 to 3 seconds) through an 18 gauge needle into a cubital vein with the subject in the supine position. The time is recorded from the beginning of injection to the perception of a bitter taste (average normal range 9 to 16 seconds)



**Tests and Standards.—**

Sodium Dehydrocholate occurs as a fine, colorless, crystalline powder with a very bitter taste, soluble in water and alcohol. An aqueous solution is alkaline to litmus.

Dissolve about 1 Gm. of sodium dehydrocholate in 200 cc. of water; add an excess of hydrochloric acid; collect the resultant dehydrocholic acid on a filter, wash, and recrystallize from 80 per cent acetic acid; it melts at 233-238 C.

Dissolve about 0.5 Gm. of sodium dehydrocholate in 100 cc. of water, acidify with hydrochloric acid and filter; Separate portions of 10 cc each of the filtrate yield no turbidity with 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm. of sodium dehydrocholate accurately weighed, to constant weight at 100 C. The loss in weight does not exceed 7 per cent. Weigh accurately about 1 Gm. in a tared platinum crucible, add 2 cc. of sulfuric acid, gently heat while fumes of sulfur trioxide are evolved, repeat, using two portions of 1 cc. of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 5.3 per cent, nor more than 5.6 per cent, when calculated to the dried substance.

**GEORGE A. BREON & COMPANY, INC.**

Ampul Solution Sodium Dehydrocholate 20% W/V:  
5 cc.

**ENNO PRODUCTS, INC.**

Ampoules Solution of Sodium Dehydrocholate 20%  
W/V: 3 cc and 10 cc.

**THE LAKESIDE LABORATORIES, INC.**

Ampules Solution of Sodium Dehydrocholate 20%  
W/V: 10 cc.

Solution of Sodium Dehydrocholate 20% W/V: 30 cc.  
vial. Preserved with 0.5 per cent chlorobutanol.

**RIEDEL-DE HAEN, INC.**

Ampoules Solution Decholin-Sodium, 20 per Cent:  
3 cc, 5 cc and 10 cc.

U S trademark 315,083.

## CHAPTER X

### CONTRACEPTIVES

When protection from pregnancy is considered advisable contraceptives are used to prevent passage of active spermatozoa from the vagina into the uterus. This is accomplished mechanically by occlusive devices such as diaphragms which lengthen the route which the spermatozoa must travel to reach the os, thereby assuring extensive exposure to a spermicidal jelly or cream. Contraceptive jellies and creams act as chemical agents immobilizing the spermatozoa with which they come into contact. Because of their consistency they also have an obstructive function. Certain accessory devices are used with these, such as inserters and extractors for the diaphragms and syringe applicators for the jellies and creams. In control of conception acceptability probably plays a greater role in the use and therefore the effectiveness of a prescription than in most fields of medicine. The esthetic block or reluctance toward various methods differs with different users and variation of method by a single user is often found to lead to greater acceptability and consequently a higher degree of protection.

#### *Contraceptive Preparations*

### CONTRACEPTIVE JELLIES AND CREAMS

*Actions and Uses*—Jellies and creams for contraceptive use are introduced into the vagina usually with an occlusive diaphragm or cervical cap not more than twelve hours before sexual intercourse. They may also be used without an occlusive device but this may result in a lower degree of protection. Some users find this technic definitely more acceptable sufficiently so to outweigh the differential in fertility rate. When so used the jelly or cream is introduced into the vagina within an hour before intercourse by a syringe applicator. The recommended dose varies but is usually approximately 5 cc. To allow adequate time for chemical immobilization the occlusive device should not be removed nor should a douche be taken within six hours after ejaculation.

As most of the contraceptive diaphragms are made of rubber which will deteriorate if exposed to greases the jellies and creams used should not contain greasy substances.

## ORTHO PRODUCTS, INC.

U. S. patent pending under serial number 360,665 Vaginal Creams  
U. S. trademark number 390,141.

**Ortho-Creme.** A nonfatty stearic acid cream having a  $p_n$  of 6, prepared from the formula:

Stearic acid.. .. .	24 00%
Stearyl alcohol .... .	0 50
Glycerin .. . . .	7.00
Ricinoleic acid..... .	0.75
Sodium lauryl sulfate..... .	0.28
Boric acid..... .	2.00
Perfume .. . . .	0 05
Water to.. . . .	100 00%

*Actions and Uses*—See preceding article, Contraceptive Jellies and Creams.

*Dosage.*—5 cc.

## ORTHO PRODUCTS, INC.

U. S. patent number 271,159 (October 5, 1943; expires 1960). U. S. trademark number 298,222.

**Ortho-Gynol Vaginal Jelly.** A water soluble jelly formed from tragacanth and acacia, having a  $p_n$  of 4.5, prepared from the formula:

Tragacanth . . . . .	3
Acacia . . . . .	0 5
Glycerin .. . . .	5
Boric acid .. . . .	3
Ricinoleic acid .. . . .	0.75
Propyl ester of parahydroxybenzoic acid.... .	0 05
Oxyquinoline sulfate .. . . .	0 025
Perfume ... . .	0 025
Water to.. . . .	100 00%

The consistency is indicated by a 55-60 mm. dart penetration at 40 C. when tested with the Braun dart penetrometer.

*Actions and Uses*—See preceding article, Contraceptive Jellies and Creams

*Dosage.*—5 cc

## CONTRACEPTIVE DIAPHRAGMS

*Actions and Uses.*—As diaphragms cannot be designed to form a junction with vaginal wall or cervix which will prevent the passage of an organism of the size of a spermatozoon, a spermicidal jelly or cream should be prescribed for use with them.

The appropriate size of diaphragm (varying from 50 to 105 mm. in diameter) must be chosen for each user. It should be as large as is comfortable, large enough to extend easily over the cervix, anchoring posteriorly in the posterior fornix

and anteriorly behind the symphysis. The appropriate size may change after a delivery and during the postpartum months. Satisfactory fitting is not possible in some cases of variant anatomy of the soft parts (this does not refer to bony structure).

The diaphragm and jelly or cream should be inserted before intercourse (not more than twelve hours before) and left in place until six hours or more after ejaculation (not more than thirty six hours). Rubber diaphragms should not be exposed to fatty substances and should be inspected from time to time for holes or tears.

#### **ORTHO PRODUCTS, INC**

U S trademark number 387 080

**Ortho Diaphragms** Latex rubber diaphragms covering a circular coiled spring the external diameter varying in gradations of 5 mm from 55 to 90 mm

#### **SYRINGE APPLICATORS FOR CONTRACEPTIVE JELLIES AND CREAMS**

**Uses**—Applicators are designed for ready filling from the container of contraceptive jelly or cream and for delivery under moderate pressure of the recommended dose (usually 5 cc) into the upper vagina. They should be transparent to permit detection of air which might lead to inadequate dosage and if made of glass should be sufficiently thick walled to make breaking while in the vagina extremely improbable. The end should be blunt and sufficiently large to prevent entry into the urethra.

#### **ORTHO PRODUCTS INC**

Registration of the trademark Ortho for measured dose applicator was issued by the U S Patent Office May 5 1942

**Ortho Vaginal Applicator** A transparent plastic syringe threaded at the blunt intravaginal end to screw onto the tubes of Ortho Gynol Vaginal Jelly or Ortho Creme to permit filling by compression of the tube. The full capacity is 5 cc the recommended dose.

#### **JULIUS SCHMID INC**

U S patent number 2 252 212

**Ramses Vaginal Applicator** A transparent plastic tube threaded at the blunt intravaginal end to screw onto the tubes of Ramses Jelly to permit filling by compression of the tube. A short plastic cylinder fitting inside the tube permits air pressure from a detachable bulb to expel the jelly. The full capacity is 5 cc the recommended dose.

**CONTRACEPTIVE DIAPHRAGM INSERTERS**

*Uses.*—Inserters are designed to stretch the circular spring of a contraceptive diaphragm into a long oval and to furnish a handle with which it may be inserted into the vagina and guided beyond the cervix. To some users they have the esthetic appeal that they minimize digital contact with jelly or cream, or genitals.

**JULIUS SCHMID, INC.**

U. S. patent number 2,252,212. U. S. trademark number 353,028

**Ramses Diaphragm Introducer.** A transparent plastic device designed to stretch and hold for insertion a diaphragm of a given size. Made in different sizes marked for diaphragms from 50 to 90 mm. in diameter in gradations of 5 mm. On the handle end is a blunt hook to assist in extracting the diaphragm.

**CONTRACEPTIVE FITTING RINGS**

*Uses.*—To enable the physician to test the size of contraceptive devices needed for a given patient, circular coiled springs of the various sizes have been prepared without the thin rubber diaphragm. As these have thick rubber coatings, repeated sterilization by boiling is possible without deterioration.

**JULIUS SCHMID, INC.**

**Ramses Fitting Rings.** Prepared in sets having sizes from 50 to 90 mm. in diameter in gradations of 5 mm.

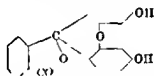
# CHAPTER XI

## DIAGNOSTIC AIDS

### External

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with phthalic anhydride ( $C_6H_4<\overset{\sim}{\underset{\sim}{CO}}>O$ ), water is eliminated and the product has the following structural formula



Fluorescein is closely related to phenolphthalein and its derivatives differing chiefly in the presence of an oxygen molecule linking the two ortho positions of the phenol nuclei. In common with the phthaleins, it forms salts with alkali whereby a rearrangement takes place and the quinoid group is formed. Fluorescein is easily brominated, the tetrabrom compound being the beautiful dye eosin.

**Actions and Uses**—The soluble sodium salt of fluorescein (fluorescein 2 Gm. sodium bicarbonate 3 Gm., water to make 100 cc.) has been used for the diagnosis of corneal lesions and

cated by a yellow hue. Fluorescein also reveals defects or disease of the endothelium of the cornea, producing a deep coloration of the diseased area.

#### Preparation and Tests—

Fluorescein is prepared by the fusion of phthalic anhydride and resorcinol at from 195 to 200 C. till the mass becomes solid. This

## Internal

*Benzoic Acid Derivatives*

**SODIUM BENZOATE.**—"When dried at 100 C for six hours, contains not less than 99 per cent of  $C_6H_5COONa$ ." U. S. P.

For standards see the U. S. Pharmacopeia under Sodium Benzoate.

**Actions and Uses.**—The intravenous use of sodium benzoate as a liver function test was suggested by Quick and his co-workers in 1938 (Quick, A. J.; Ottenstein, H. N., and Weltcheck, Herbert; *Prac. Sac. Exper. Biol. & Med.* 38:77 [Feb.] 1938) to overcome the disadvantages associated with its oral administration. In the presence of normal liver function in man, benzoic acid is excreted as hippuric acid. The rate at which this material is excreted determines the functional ability of the liver and often demonstrates the presence of liver damage before clinical signs are evident.

The test is contraindicated in the presence of renal disease, because here the hippuric acid is but partially eliminated.

**Dosage.**—The bladder is emptied before administration of the drug. Inject *slowly*, intravenously, 20 cc. of sodium benzoate solution containing 1.77 Gm. of the salt (equivalent to 1.5 Gm. of benzoic acid), using not less than five minutes for the injection. Exactly one hour after the injection a complete urine specimen is collected and the amount of hippuric acid determined by the method developed by Quick (Quick, A. J.; *Am J. Digest. Dis.* 6:716 [Dec.] 1939).

An adult with a normal liver will excrete at least 1 Gm. of hippuric acid (equivalent to 0.68 Gm. of benzoic acid) within one hour after receiving sodium benzoate intravenously.

GEORGE A. BREON & COMPANY, INC., KANSAS CITY, Mo.

Ampul Sodium Benzoate Solution: 1.77 Gm (equivalent to 1.5 Gm benzoic acid) in 20 cc.

*Barium Sulfate*

**BARIUM SULFATE.**—For description and standards see the U. S. Pharmacopeia under Barium Sulfate.

**Caution.**—When Barium Sulfate is prescribed, the title should always be written out in full to avoid confusion with the poisonous barium sulfide or sulfite. U. S. P.

**Actions, Uses and Dosage.**—Barium sulfate for roentgen examination, being freed from soluble barium and other salts, passes unchanged through the digestive tract and because of this is used in taking roentgenograms of the stomach and of the intestines.

*For Roentgen Examination of the Stomach*—A barium sulfate suspension is made containing 300 Gm of pure barium sulfate in 400 cc of water

*For Roentgen Examination of the Colon*—A barium sulfate suspension is made containing 750 Gm of barium in 1,500 cc of water

The patient should be prepared by the administration of 1 ounce of castor oil the night before the examination and of a plain water or saline enema two hours before the procedure is performed

The suspension warmed to body temperature is injected into the rectum by enema tube from a height of 90 to 180 cm

#### MALLINCKRODT CHEMICAL WORKS

Barium Sulfate for X-Ray Diagnosis bulk

#### MERCK & Co, INC

Barium Sulfate for X-Ray Diagnosis bulk

*Skiabaryt for Oral Administration* A mixture of barium sulfate, 80 to 85 per cent sugar tragacanth vanillin cinnamon and cacao

U S trademark 163 022

*Dosage* Triturate 150 to 200 Gm (5 to 6.5 ounces) with cold water added gradually to form a smooth thin paste then add warm water gradually until the mixture measures 500 cc (16 fluidounces) The mixture is then ready for drinking

*Skiabaryt for Rectal Administration* A mixture of barium sulfate U S P, 80 to 85 per cent, sugar and tragacanth

*Dosage* Mix 200 Gm (6.5 ounces) with cold water to form a smooth paste then add warm water with stirring until the mixture has acquired a fairly fluid consistency It is then ready for administration through the irrigator

#### E R SQUIBB & SONS

Barium Sulfate for Roentgen-Ray Work. bulk

#### *Iodized Oils*

Iodized oils are injected as contrast mediums in roentgen diagnosis especially of tumors of the spinal cord, in the localization of bronchial and pulmonary lesions, and in gynecology Various vegetable oils may be used, animal oils cause local irritation According to the method of iodation, the oil may contain iodine alone, or iodine and chlorine ('chloriodized oils') These do not differ essentially

Iodized oils are quite viscid For injections into cavities they may be rendered less viscid by the addition of ethyl oleate, they may be rendered water miscible by emulsification

*Caution*—"It should be emphasized that the injection of iodized oils is essentially a surgical procedure, introducing a foreign and possibly irritant body, and involving more or less risk, which should be weighed against the presumptive advan



tages, in comparison with the relative advantages and disadvantages of other measures. The following cautions should be especially borne in mind:

"1. Oils that have aged and darkened beyond their original color should never be used.

"2. Subarachnoid injections should be avoided, at least until all other means of diagnosis have been exhausted.

"3. Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of respiratory area would be contraindicated.

"4. The injection pressure should be carefully controlled, so as not to lacerate the tissues.

"5. Intra-uterine injections should be made only under fluoroscopic observations.

"6. Iodized oil should not be used for renal pyelography, except in the form of emulsion; and the injection should be stopped if pain is felt.

"7. Intravascular injections with iodized oil appear too dangerous; the use of emulsions for this purpose requires further study." (Dangers of the Injection of Iodized Oils, Report of the Council on Pharmacy and Chemistry. *The Journal*, A. M. A. 99:1946, Dec 3, 1932. The full report may be consulted for further discussion of the history, scope and limitations of iodized oils.)

8. When the so-called per-nasal method of injecting the oil into the larynx is employed, it is remembered that in the injection of the local anesthetic, the risk of intoxication from the anesthetic is increased as the absorptive surface is increased.

**LIPIODOL 40% IODINE.**—Iodized Poppy-Seed Oil 40 per cent.—An iodine addition product of poppy-seed oil containing 39 to 41 per cent of iodine (0.54 Gm. of iodine per cc.) in organic combination

**Actions and Uses.**—Lipiodol 40% iodine is used as a substitute for inorganic iodides; and as a contrast medium in roentgenography. See preceding article, Iodized Oils. In subarachnoid injection for roentgen examination, lipiodol radiologique descendant is used for the recognition of intradural tumors.

**Dosage.**—From 1 cc. to 5 cc. or more according to the uses to which it is to be put.

#### **Tests and Standards—**

Lipiodol 40% iodine is a thick, viscous oily liquid, which possesses a althaceous odor and an oleaginous taste and is insoluble in water. On exposure to air and sunlight it decomposes, turning a dark brown color. Its specific gravity at 20 C., is from 1.340 to 1.350.

Boil 0.5 cc. of lipiodol 40% iodine and 10 cc. of alcoholic solution of potassium hydroxide (1 in 10), in a porcelain dish for about five minutes, evaporate the liquid on a water bath and ignite the residue

Dissolve the residue in 10 cc of water, filter the solution add 5 cc. of hydrochloric acid to the filtrate, then add chloroform and a few drops of chlorine water and agitate the chloroform solution is violet. Dissolve 1 cc of lipiodol and add 5 cc of water, add a few drops of phenolphthalein solution, add 10 cc of 10% sodium hydroxide solution, add 10 cc of lipiodol, the solution is violet, parent liquid results.

Boil about 1 cc of lipiodol 40% iodine with 10 cc. of nitric acid and 0.5 Gm of silver nitrate, cool, add 25 cc of water, collect the precipitate formed on a filter paper, wash free from the excess of silver nitrate, puncture the filter, collect its contents in a glass stoppered flask, treat with 50 cc of stronger ammonia water, agitate thoroughly and allow to stand for one hour. Filter off the insoluble silver iodide, treat the filtrate with 15 cc potassium iodide solution and remove the excess of ammonia by evaporation on a steam bath, no opalescence results (absence of chlorine compounds).

Ignite about 1 Gm accurately weighed, the residue does not exceed 0.01 per cent. Transfer about 0.35 Gm accurately weighed to a bomb tube, determine the iodine content by the Carius method, the amount of iodine found is not less than 39 per cent nor more than 41 per cent.

#### E. FOUGERA & Co, INC.

Ampoules Lipiodol 40% Iodine 1 cc, 2 cc., 3 cc. and 5 cc

Lipiodol, 40%, Iodine 20 cc neoprene capped flask

Lipiodol 40%, Iodine Radiologique Descendant 5 cc. flasks

U S trademark 196,499

**LIPIODOL RADIOLOGIQUE ASCENDANT**—Iodized Poppy-Seed Oil 10 per cent.—An iodine addition product of poppy-seed oil containing 9.8 to 11.2 per cent of iodine (0.11 Gm of iodine per cc) in organic combination.

**Actions and Uses**—Lipiodol radiologique ascendant is used for recognition of intradural tumors when it is desired to employ a contrast medium of lesser density than that of the spinal fluid.

**Dosage**—From 1 to 2 cc. previously brought with the syringe, to a temperature of 40 C.

#### Tests and Standards—

Lipiodol radiologique ascendant is a yellow oily liquid which possesses an alliaceous odor and an oleaginous taste and is insoluble in water. On exposure to air and sunlight it decomposes turning brown in color. Its specific gravity at 20 C is from 0.99 to 1.

Lipiodol radiologique ascendant conforms to the tests for identity and purity, ash and assay as described under Lipiodol Lafay except that the iodine content found is not less than 9.8 per cent nor more than 11.2 per cent.

#### E. FOUGERA & Co, INC.

Lipiodol Radiologique Ascendant 5 cc flasks

U S trademark 196,499

**LIPOIODINE.** — Iodobrassid. — Ethyl diiodobrassidate  $C_{27}H_{39}I_2COO(C_2H_5)$ , the ethyl ester of diiodobrassicidic acid  $CH_3(CH_2)_7CHI.CHI.(CH_2)_{11}COOH$ , containing 41 per cent of iodine

*Actions and Uses.*—Lipoiodine is used as a substitute for the inorganic iodides and as a contrast medium for roentgenologic work. See preceding article, Iodized Oils

For diagnostic work, from 5 to 20 cc. of lipoiodine diagnostic, as determined by the extent of the field to be investigated.

*Tests and Standards.*—

Lipoiodine crystallizes in white, odorless and tasteless needles, melting at 37 C. It is insoluble in water, slightly soluble in alcohol, and very soluble in fatty oils, ether and benzene. Lipoiodine is decomposed by exposure to direct light

The iodine content of lipoiodine is from 40.5 per cent to 41.5 per cent

**GIBA PHARMACEUTICAL PRODUCTS, INC.**

**Lipoiodine Diagnostic:** 10 cc. bottle A 60 per cent solution of lipoiodine in sesame oil

U. S. patent 1,024,171 (April 23, 1912; expired).

U. S. trademark 81,554

**Water-Soluble Organic Iodine Compounds for Roentgenography**

Satisfactory roentgenograms of the urinary tract may be secured by the intravenous injection of soluble iodine compounds of low toxicity, which are rapidly excreted by the urine. Several organic compounds are now available for this use. Sodium iodide, in the necessary dose, is too toxic for intravenous injection. The organic compounds may also be used for ureteral retrograde pyelography.

For intravenous urography, it is now generally accepted that no fluids should be given to the patient for several hours (usually from midnight) prior to examination. Restriction of fluids permits greater concentration of the drug. The gastrointestinal tract should be cleared of gas and retained materials by enemas and laxatives, preferably of castor oil. The excretory urogram should be made by those who are experienced with this method and during the entire procedure the patient should be watched for untoward reactions. Recently, Asher and Harris have described an ocular test for sensitivity to diodrast, (*Am. J. Roent.* 48:762, 1942). The medium should be given slowly, pausing after 1 or 2 cc. are injected to see if a reaction may occur. Care should be exercised to ensure that all the solution is injected into the vein. Side effects which may be encountered include flushing of the face and neck, urticaria, fall in blood pressure, nausea, vomiting, lacrimation, salivation, edema of the glottis, bouts of coughing, "tight feeling" or choking sensation,

and cyanosis. Usually these symptoms disappear over varying periods of time but fatalities have been encountered. Any history of allergy should be elicited before injection. If there is reason to suspect that a reaction may occur a small initial dose may be given first. In any event epinephrine hydrochloride 1:1,000 should be available when the injection is made. The intra-

pyelography, and either or both methods closely correlated with the clinical findings. Injection of the medium into the kidney pelvis is most accurately gauged by using a manometer, but lacking this instrument gravity or a syringe may be employed for retrograde pyelography if care is exercised. Because of reflex splanchnic stimulation, anuria especially after bilateral examination has been reported. Excretory urography or retrograde pyelography should not be repeated too soon.

The compounds may be used for venograms in the study of varicose veins.

**DIODR** — — — — —  
 done-*N*-acet — — — — —  
 —Diodrast — — — — —



**Actions and Uses.**—Diodrast is used as a contrast agent for intravenous urography. Local reactions about the site of injection are absent or very mild, systemic reactions occur occasionally. The latter consist chiefly of flushing of the skin with a sense of warmth, less often transient nausea, vomiting, erythematous eruptions, respiratory distress and cyanosis. These side effects usually subside within a few minutes to an hour or so without special therapy, but the skin eruptions may rarely persist for several days. In animals diodrast in doses equivalent by weight to those used clinically has been found to lower the blood pressure for a period of about two hours, this slowly returns to normal and may be followed by a secondary rise. Respiration is stimulated. These actions have been reported also to occur in human subjects. Fasting and dehydration of patients preliminary to injection of the drug are widely employed. The optimum time for taking roentgenograms varies between five and fifteen minutes after injection in individuals with normal kidney function (usually one exposure is made after ten minutes and a second after a further interval).

of ten or fifteen minutes). When renal function is impaired the interval is proportionately longer (thirty minutes or more). A safe routine is to take roentgenograms at 5, 15 and 45 minutes after injection of the drug. Pressure over the bladder is employed by some clinicians; this is released immediately before the first exposure and is replaced until the next. The use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe anemia and it should be used with caution in cases of elevated blood pressure and hypertension. Preliminary renal and hepatic function tests are advisable in suspected cases. Caution should be exercised in cases in which a reduction in blood pressure would be dangerous.

**Dosage.**—Di. contrast is administered intravenously in the form of an aqueous solution; each cubic centimeter contains 0.15 Gm. Twenty cc. of a solution containing 7 Gm. of di. contrast, previously warmed to body temperature, is injected slowly, usually into the cubital vein. Children are given correspondingly smaller doses. It may be administered intramuscularly or subcutaneously in infants, children, and adults with inoperable or dilated aortic aorta, and sometimes in uncooperative, restless patients.

#### Tests and Standards.—

Di. contrast responds to the following identity tests: Dissolve about 10 cc. of di. contrast solution with an equal volume of water, add an excess of diluted hydrochloric acid, collect the liberated di. contrast gas over No. 40 and 41 on a filter paper, wash and dry at 110 C.; it melts with decomposition between 215 and 219 C. (the melting point both previously heated to 212 C.). (Save the filtrate.) Transfer about 0.1 Gm. of the residue and to a small hard glass test tube containing a piece of sodium (about the size of a pea), previously melted, after the first violent action has ceased, heat until the contents of the test tube are decomposed; vapors of iodine are evolved, the tube and contents are allowed to cool, add 10 cc. of water; boil the mixture for a few minutes, filter through paper and divide into two portions, to one portion add 1 cc. of concentrated nitric acid, heat, cool and add 1 cc. of silver nitrate solution; a curdy yellow precipitate results, insoluble in an excess of stronger ammonia water; to the other portion add a few drops of fresh sodium and ferrous sulfate solutions, heat to nearly boiling and carefully neutralize with diluted hydrochloric acid; a finely divided blue precipitate results. Concentrate the original filtrate from the foregoing, cool to the water, filter, evaporate to syrupy consistency, add 5 cc. of alcohol, neutralize the mixture carefully with normal sodium hydroxide using litmus as an indicator, filter and increase the volume of the filtrate to about 10 cc. with absolute alcohol, add 1 Gm. of trimetaphenol (picric acid), heat to boiling and finally cool in ice water, collect the resulting dark-brown trimetaphenolate on a filter paper, recrystallize from alcohol and dry in a desiccator over sulfuric acid under a partial vacuum; it melts at 109 to 110 C.

Dissolve about 1 Gm. of the resultant acid in 1.5 cc. of a 10 per cent solution of sodium hydroxide and make up to a volume of 5 cc.; a clear colorless solution results. To the foregoing solution add 7 cc. of water and an excess of diluted hydrochloric acid, filter, and divide the filtrate into two portions, to one portion add 1 cc. of chloroform and 0.1 cc. of ferric chloride solution; no coloration is imparted to the chloroform layer (absence of free inorganic iodides), to the other portion add 1 cc. of barium chloride solution; no turbidity results (sulfate).

*D* odo-4 pyridone *N*-acetic acid a component of diodrast responds to the following tests for identity and purity

*D* iodo-4 pyridone *N*-acetic acid occurs as a white crystalline odorless powder slightly soluble in water practically insoluble in organic solvents. It melts at 245 to 249 C with decomposition (the melting point bath previously heated to 200 C)

*D* odo-4 pyridone *N*-acetic acid responds to identity and purity tests previously described under diodrast except those dealing with diethanolamine

Dry about 1 Gm of diodrast acid component 35 *d* odo-4 pyridone *N*-acetic acid accurately weighed to constant weight at 100 C the loss in weight does not exceed 1 per cent. Transfer about 1 Gm of Diodrast acid component accurately weighed to a 500 cc Kjeldahl flask and

described in

caption of (

2 paragraph

than 3.3 nor more than 3.6 when calculated to the dried substance. Transfer about 0.5 Gm of the diodrast acid component to a Parr sulfur bomb determine the iodine content by the Lemp and Brodersen Method (*J. A. Chem. Soc.* 38: 2069) the amount of iodine found corresponds to not less than 67.3 per cent nor more than 63.2 per cent when calculated to the dried substance

**DIODRAST STERILE SOLUTIONS** Diodrast solution is prepared by neutralizing 35 *d* odo-4 pyridone *N*-acetic acid in water with an equivalent quantity of diethanolamine. The mixture thus formed in solution (not isolated in solid form) is very soluble in water.

Diodrast solution occurs as a clear and nearly colorless liquid. It is neutral to litmus. Diodrast solution is incompatible with mineral acids. The specific gravity is from 1.180 to 1.190 at 25 C.

Place 10 cc of diodrast solution accurately measured in a suitable tared platinum dish evaporate to dryness on the steam bath and ignite the residue does not exceed 0.10 per cent.

Transfer 10 cc of diodrast solution accurately measured to a 100 cc volumetric flask add water to the mark and mix. Place 10 cc of the diluted solution in a 50 cc beaker. Heat gently to boiling and add exactly 12 cc of approximately tenth normal silver nitrate. Stir until the precipitate becomes granular cool in ice water for thirty minutes with occasional stirring filter through a tared Gooch crucible using the cold filtrate to wash the beaker and wash the precipitate with 5 cc of ice cold water dry to constant weight at 110 C. To the weight of the precipitate (silver salt of 35-*d* odo-4 pyridone *N*-acetic acid) found add 0.00135 Gm as a solubility correction the resultant is not less than 0.344 Cm nor more than 0.358 Cm.

## WINTHROP CHEMICAL COMPANY, INC.

### Diodrast

**Ampules Diodrast Sterile Solution (35 per Cent W/V)** 10 cc 20 cc and 30 cc

U. S. Patent No. 1,993,039 (March 3, 1935 expires 1951) is a trademark J12451

**DIODRAST COMPOUND SOLUTION**—An aqueous solution containing approximately 40.5 per cent (W/V) of the diethanolamine salt of 35 *d* odo-4 pyridone *N*-acetic acid and approximately 9.5 per cent (W/V) of the diethylamine salt of 35 *d* odo-4 pyridone *N*-acetic acid. Diodrast compound solution contains about 25 per cent (W/V) of iodine in organic combination.

**Actions and Uses.**—Diodrast compound solution is employed for roentgenographic visualization of the urinary tract by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It is designed to provide a relatively large amount of iodine in a small volume of solution particularly for injection of obese subjects or for patients who cannot or will not cooperate in the preliminary preparation for excretion urography with diodrast. Roentgenograms should be taken at 5, 15 and 45 minute intervals after injection of the drug. Delayed, incomplete or absent shadows are given the same interpretation as when diodrast is employed. The same contraindications and precautions should be observed as for diodrast.

**Dosage.**—For excretion urography, diodrast compound solution is administered intravenously in sterile aqueous solution, the average dose for adults being 20 cc. Diodrast compound solution may be employed without dilution for retrograde pyelography. For economy, more dilute solutions are customarily used with satisfactory results. Eight cc. of diodrast compound solution (50 per cent concentration of radiopaque material) when diluted with 12 cc. of sterile distilled water yields 20 cc. of 20 per cent concentration. Five cc. of diodrast compound solution diluted with 15 cc. of sterile distilled water (final concentration 12.5 per cent) gives wholly satisfactory pyelograms; this dilution is generally employed with excellent results in thin individuals. The volume of fluid generally required for retrograde examination in adults is 20 cc.

#### *Tests and Standards*—

Diodrast compound solution is prepared by neutralizing 3,5-diiodo-4 pyridone-N-acetic acid in water with appropriate quantities of diethanol amine and diethylamine. The mixture thus formed (not isolated in solid form) is soluble in water.

Diodrast compound solution occurs as a clear, pale yellow, odorless liquid, possessing a bitter taste. It is neutral to litmus and is incompatible with mineral acids and heavy metal salts. Its specific gravity is about 1.270 at 25 C.

Dilute about 0.5 cc. of diodrast compound solution to 5 cc. with water and acidify with hydrochloric acid; collect the precipitate on a filter, wash with cold water and dry at 100 C.; the 3,5-diiodo-4 pyridone-N-acetic acid obtained melts at 245-249 C., with decomposition (the melting point bath previously heated to 200 C.).

Dilute about 10 cc. of diodrast compound with 20 cc. of water; acidify with hydrochloric acid and filter off the precipitate. To the filtrate add 5 cc. of approximately 50% sodium hydroxide solution and distil into about 25 cc. of normal hydrochloric acid. Evaporate the solution containing the distillate to dryness on a water bath; recrystallize the residue from alcohol by the addition of diethyl ether; dry the product under partial vacuum; the melting point of the diethylamine hydrochloride obtained is from 224 to 227 C. with sublimation.

Acidify the alkaline residue remaining in the distilling flask with dilute hydrochloric acid, remove the solution from the flask and evaporate to about one third of its volume. Cool the concentrated solution in ice water for fifteen minutes with occasional shaking, filter and concentrate the filtrate to a syrup. Treat the syrupy residue with 5 cc. of absolute alcohol, neutralize dropwise with normal sodium hydroxide, filter, wash and finally dilute the filtrate to about 8 cc. with alcohol. Add about 0.5 Gm. of picric acid (trimetaphenol) to the solution, boil,

cool and place in the ice chest. Collect the precipitate on a filter recrystallize from absolute alcohol and dry under partial vacuum the melting point of the diethanolamine triisotrophenolate obtained is between 109 and 110 C.

Dilute 20 cc of diodrast compound solution accurately measured, to 200 cc. in a calibrated flask. Use portions of the diluted solution in the following determinations:

Evaporate 20 cc of the diluted solution accurately measured, in a tared platinum dish on a water bath and dry to constant weight at 100 C. the weight of the residue is equivalent to not less than 48 per cent (W/V) nor more than 51 per cent (W/V) calculated to the original solution. Ash the residue in the presence of sulfuric acid the weight of the ash obtained is equivalent to not more than 0.1 per cent.

Transfer 20 cc of the diluted solution to an ammonia distillation apparatus, add 50 cc. of water 5 cc. of 50 per cent sodium hydroxide and distil into 30 cc. of fifth normal hydrochloric acid. Titrate the

Acidify the residue remaining in the Kjeldahl flask used in the foregoing determination with sulfuric acid. Concentrate the mixture and digest with 10 cc of sulfuric acid and 0.05 Gm. of selenium metal until clear. Cool, dilute with 100 cc of water transfer to the ammonia distillation apparatus and add an excess of 50 per cent sodium hydroxide. Distil into 50 cc of tenth normal hydrochloric acid and titrate the excess acid with tenth normal sodium hydroxide using methyl red as the indicator. The amount of tenth normal hydrochloric acid consumed by the distillate is equivalent to the ammonia derived

From the amount of 3,5-diiodo-4 pyridone-N-acetic acid 10.000, calculate the equivalent in cc of tenth normal hydrochloric acid for 2 cc. of the original solution. Deduct this number of cc of tenth normal hydrochloric acid from the number used in the titration of the total ammonia from the Kjeldahl determination. The difference calculated to a diethanolamine should be not less than 8.2 per cent (W/V) nor more than 8.7 per cent (W/V).

WINTHROP CHEMICAL COMPANY, INC.

Ampul Diodrast Compound Solution 20 cc, 30 cc

U S Patent No 1 993 039 (March 5 1935 expires 1952) U S  
Trademark No 312 451

**DIODRAST CONCENTRATED SOLUTION.**—An aqueous solution containing 70 per cent (W/V) of the diethylamine salt of 3, 5-diiodo-4 pyridone-N acetic acid.

**Actions and Uses.**—Diodrast concentrated solution is employed for use in a special diagnostic procedure for visualization of the heart, the ascending and descending aorta and branches the superior vena cava, the pulmonary artery and branches the



coronary arteries and other structures of the heart and mediastinum. It has also been used for cholangiography by injection of the material into the common bile duct. The technic in using this agent is relatively complicated and requires accurate timing and teamwork between the physician, the patient and the roentgenologist. The method consists in injecting the substance into the blood and taking roentgenograms simultaneously with the concentration of the opaque material in the cardiopulmonary system. In addition a preliminary examination of the chest with the x-rays is necessary to obtain data for roentgenography. At times it is necessary to determine the circulation rate of the blood for accuracy. The contraindications include hepatic disease, nephritis and hyperthyroidism. The drug should be used cautiously in the presence of heart disease and circulatory failure, never in those patients who are critically ill or in collapse. Preliminary renal function tests and determination of the patients' sensitivity should be carried out. Those with an idiosyncrasy should not be given the drug. To lessen nausea and vomiting the stomach should be empty. Side effects include dizziness, nausea, vomiting, sense of intense warmth, sweating, pallor, hypotension, transient pain at the site of injection, headache, fever, chills, cyanosis, etc. Delayed reactions may occur. Premedication with a barbiturate is advisable; epinephrine is administered when there is a possibility of an allergic reaction or low blood pressure. This technic can be mastered by experienced workers who have the proper facilities, although it might be dangerous in the hands of persons who are inexperienced or by those who use the technic in a casual manner. In skilled hands untoward reactions are comparatively few. It is claimed by the manufacturer this agent is sufficiently stable to permit boiling for a time if a question of sterility should arise, although the is marketed in sterile form.

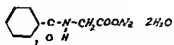
*Dosage.*—Diodrast concentrated solution should not be used intravenously only in those cases which present diagnostic problems. The amount varies according to the size of the chest, the size of the patient and body weight. For cardiopulmonary visualization 45 cc. may be injected intravenously. When the pulmonary circulation is desired, 30 cc. is sufficient. If the intravenous injection must be delayed, 15 minutes should elapse. The duration of the effect is from one and one-half to two seconds. The agent must not be injected into the tissue outside the vein. The result is not permanent. If crystals are present warm the solution before using.

For cholangiography the amount of the solution varies within wide limits. As much as 100 cc. has been required to fill the common bile duct.

WINTHROP CHEMICAL COMPANY, INC

Diodrast Concentrated Solution (70 Per Cent W/V)  
35 cc vial

when calculated to the dried substance



*Actions and Uses*—Hippuran is proposed for use as a radiopaque agent for intravenous oral or retrograde urography. When used by the intravenous route, irritation at the site of injection is stated not to occur and systemic reactions appear to be unusual, a sensation of generalized warmth is the most common side effect. Nausea occurs occasionally and vomiting rarely. Fasting and dehydration of patients preliminary to administration of the drug are usually employed. Pressure over the bladder region is employed by some clinicians, this is released immediately before the first exposure and is replaced until the next. Ordinarily the first film is exposed about ten minutes after injection and two subsequent pictures are taken at fifteen or twenty minute intervals. In case excretion is delayed, later exposure may be necessary.

Results with oral administration of the drug are less satisfactory but a sufficiently high percentage of successful pictures appear to be obtained to make this method worthy of trial in cases of acute or chronic renal disease or retrograde urography.

The use of moderate compression over the bladder region is recommended in the intervals between exposures. While the

be employed

Satisfactory visualization has been reported with hippuran when employed by the retrograde method for urethrograms, cystograms or pyelograms. There is said to be little or no tissue irritation with effective concentrations.

*Dosage*—For intravenous use 25 cc of a solution containing 12 Gm of hippuran previously warmed to body temperature is injected into the cubital vein. Young children are given proportionately smaller doses. For oral use, 12 Gm of hippuran

is dissolved in 75 cc. of simple syrup. For children, 10 Gm. is employed. For retrograde use, hippuran is employed in 15 to 20 per cent solution for pyelography or 3 to 5 per cent solution for cystography. The solution may be made either by diluting the ampule solution with sterile distilled water or by dissolving the crystals in distilled water, filtering and sterilizing by heat.

### Tests and Standards.—

Hippuran occurs as a white, crystalline powder, possessing a faint odor and an alkaline taste; very soluble in water, freely soluble in ethyl alcohol and soluble in dilute alkali. An aqueous solution is neutral or faintly alkaline to litmus.

Fuse about 0.2 Gm. of hippuran with 2 Gm. of powdered sodium hydroxide; it decomposes with the evolution of iodine vapors and ammonia. Dissolve about 0.5 Gm. of hippuran in 100 cc. of water, add an excess of dilute hydrochloric acid; the resultant *o*-iodo-

hippuric acid, C.: it melts at 171 to 174 C., to 10 cc. of uranyl zinc acetate solution.

Transfer about 0.5 Gm. of hippuran to a glass stoppered cylinder, add 25 cc. of a diluted nitric acid (one part diluted nitric acid and 5 parts water), shake for five minutes, filter: the filtrate yields no distinct opalescence on the addition of 2 cc. silver nitrate solution (*absence of inorganic halides*).

Dissolve about 0.5 Gm. of hippuran in 50 cc. of water, add 5 cc. diluted hydrochloric acid, filter: separate portions of 10 cc. each of the filtrate yield no turbidity on the addition of 1 cc. of barium chloride solution (*sulfate*), no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm. of hippuran, accurately weighed, to constant weight at 100 C.: the loss in weight is not more than 10 per cent nor less than 6 per cent. Boil about 1 Gm. of hippuran, accurately weighed, with 10 cc. of benzene for fifteen minutes, replacing the evaporated liquid if necessary, decant the supernatant liquid through filter paper and wash filter with 10 cc. and 5 cc. portions, respectively, evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 100 C.: the residue does not exceed 0.2 per cent (*uncombined o-iodohippuric acid*). Transfer about 0.5 Gm. of hippuran, accurately weighed, to a 500 cc. Kjeldahl flask; determine the nitrogen content according to the official method described in the Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 4.1 per cent, nor more than 4.4 per cent when calculated to the dried substance. Weigh accurately about 1 Gm. of hippuran in a tared platinum dish, add 5 cc. of sulfuric acid, heat cautiously while fumes of iodine and sulfur trioxide are evolved, repeat twice, using portions of 1 cc. each of sulfuric acid; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the sodium found corresponds to not less than 6.8 per cent nor more than 7.3 per cent, when calculated to the dried substance. Transfer about 0.5 Gm. of hippuran to a Parr sulfur bomb, determine the iodine content by the Leco-Broderson method (*J. Am. Chem. Soc.* 30:2069): the amount of iodine found corresponds to not less than 38.5 per cent nor more than 39 per cent, when calculated to the dried substance.

### MALLINCKRODT CHEMICAL WORKS

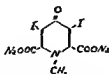
Hippuran (Powder): bulk

Hippuran Crystals. 12 Gm., 100 Gm. and 500 Gm. bottles

Sterile Solution Hippuran: 12 Gm. in 25 cc.

U. S. patent 2,135,474 (Nov. 1, 1938; expires 1955) U. S. trademark 314,577

NEO-IOPAX —Neo Iopax Sodium —Disodium *N*-methyl  
3,5-diiodo-4  
COONa Ti  
acid Neo Ic



*Actions and Uses*—Neo iopax is used as a contrast medium in intravenous urography and retrograde pyelography. Clinical reports indicate that systemic reactions occur uncommonly and are usually mild and fleeting. In some cases there is more or less severe pain in the arm radiating to the shoulder, usually this disappears on completion of the injection but in a small percentage of cases it may persist for a variable period. The pain may usually be relieved by local applications of heat and the administration of an analgesic when necessary. Fluid intake should be restricted for about twelve hours prior to the examination. If only anatomic information is desired it is usually sufficient to take a single roentgenogram from ten to twenty minutes after injection. In other cases a series of roentgenograms are taken at intervals of five, fifteen and thirty minutes after injection. It is advisable to take a film over the urinary bladder area when making the roentgenogram thirty minutes after the injection. If the first plates show that but little of the drug has been excreted, it is presumed that the kidneys are functioning poorly, and several hours should be allowed to elapse, during which plates should be made at intervals. Impairment of renal function will allow but poor concentration of the drug, many hours are then required for its excretion. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia and it should be used with caution in cases of tuberculosis and hyperthyroidism. Caution must also be exercised in patients with any severe systemic disease. Preliminary liver and kidney function tests are advisable in suspected cases.

*Dosage*—Twenty cc of solution containing 15 Gm of neo iopax previously warmed to body temperature is injected intravenously, very slowly into the cubital vein. Children are given correspondingly smaller doses.

#### *Tests and Standards*—

Neo-Iopax occurs as a white crystalline odorless powder very soluble in water, insoluble in acetone, benzene, chloroform, ether and purified petroleum benzine. An aqueous solution is neutral to litmus.

Dissolve about 0.5 Gm of neo-iopax in 100 cc of water, add an excess of diluted hydrochloric acid, collect the liberated *N*-methyl-3,5-diiodo-4-pyridoxyl-2,6-dicarboxylic acid on a filter, wash and dry in

a desiccator over sulfuric acid under a partial vacuum: it melts at about 174 C., with decomposition: heat the remainder of the resultant acid at its decomposition temperature (about 175 to 180 C.) until no further evolution of gas is noted: the residual substance, *N*-methyl 3,5-diiodo-4-pyridone, thrice recrystallized from water, melts at 214 C.; to 1 cc. of the foregoing filtrate add 10 cc. of uranyl zinc acetate solution: a yellow precipitate results. Dissolve about 0.5 Gm. of neo-iopax in 50 cc. of water, add an excess of hydrochloric acid, filter through paper and divide into two portions: to one portion add 1 cc. of chloroform and 0.1 cc. of ferric chloride solution: no chlorination is imparted to the chloroform layer (*absence of free inorganic iodide*), saturate the other portion with hydrogen sulfide: no coloration or precipitation results (*salts of heavy metals*).

Dry about 1 Gm. of neo-iopax, accurately weighed to constant weight at 100 C.: the loss in weight does not exceed 2 per cent. Transfer about 1 Gm. of neo-iopax, accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, page 24, chapter 2, paragraph 22; the percentage of nitrogen corresponds to not less than 27 per cent, nor more than 29 per cent when calculated to the dried substance. Weigh accurately about 0.5 Gm. of neo-iopax in a tared platinum dish, add 10 cc. of sulfuric acid, gently heat while fumes of iodine and sulfur trioxide are evolved, repeat, using two portions of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate: the sodium found corresponds to not less than 92 per cent nor more than 94 per cent when calculated to the dried substance. Transfer about 0.2 Gm. of neo-iopax to a Parr sulfur bomb; determine the iodine content by the Lemp and Broderick Method (*Journal of the American Chemical Society* 39:2069); the amount of iodine found corresponds to not less than 51 per cent nor more than 53 per cent when calculated to the dried substance.

## SCIHERING CORPORATION

**Ampoule Solution Neo-Iopax:** 10 cc. and 20 cc. Each 1 cc. contains 0.75 Gm. of neo-iopax in sterile distilled water.

**Ampoule Solution Neo-Iopax:** 10 cc. and 20 cc. Each cc. contains neo-iopax 0.5 Gm., dissolved in sterile distilled water.

U. S. patent 1,919,417 (July 25, 1933; expires 1950). U. S. trade mark 297,925.

**SKIODAN.**—Skiodan Sodium.—Methiodal— $\text{CH}_3\text{I SO}_3\text{Na}$ —The sodium salt of mono-iodo-methanesulfonic acid. Skiodan contains 52 per cent iodine.

**Actions and Uses.**—Skiodan is proposed as a therapeutically indifferent medium for roentgenography, especially for visualization of the urinary tract either by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It exerts a diuretic action, most marked during the first half hour after intravenous injection. Excretion studies show that within a few minutes after intravenous injection the concentration of skiodan in the urine reaches a maximum of from 4 to 6 per cent (corresponding to from 2 to 3 per cent of iodine). Usually, 75 per cent is eliminated in three hours, more than 90 per cent in ten hours, and the remainder within about twenty-four hours.

The intravenous use of the drug is contraindicated in advanced renal destruction with severe uremia, severe liver disorders and exudative diathesis in children. Caution should be exercised in hyperthyroidism and tuberculosis.

**Dosage**—For intravenous urography, skiodan is administered in sterile aqueous solution (from 20 to 40 Gm in 100 cc) the average dosage for adults being about 2 Gm for each 15 pounds of body weight, for retrograde pyelography an aqueous solution of skiodan (from 10 to 20 Gm in 100 cc) is injected through a ureteral catheter in the renal pelvis. Cystograms may be made with 3 to 5 per cent solutions. Aqueous solutions of skiodan should be kept protected from light, they can be kept for a considerable time without impairment but should be resterilized before use.

For retrograde pyelography a 15 per cent or 20 per cent skiodan solution (by volume) is used. In thin patients a 10 per cent concentration often suffices. The injection is made in the customary manner through the ureteral catheter. In cases of suspected stone some urologists prefer a 5 per cent or 6 per cent solution for thin persons to assure satisfactory contrast. In the preparation of skiodan solutions for retrograde pyelography distilled water should be used. The solution should be sterilized by boiling or autoclaving.

On the day before the intravenous injection of skiodan the patient is given a soft diet with a cleansing enema in the evening. During the night the fluid intake is restricted as much as possible.

#### *Tests and Standards—*

Skiodan occurs as a white crystalline odorless powder possessing

addition of an equal volume of zinc uranyl acetate solution (prepared according to Barber and Kolthoff, J. A. C. S. 50, 1625, 1928), a yellow crystalline precipitate results. Dissolve about 1 Gm of skiodan in 25 cc of water; separate portions of 5 cc each yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (inorganic iodide and chloride), no turbidity with 1 cc of diluted hydrochloric acid and 1 cc of barium chloride solution (sulfate), no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals). When tested for arsenic according to the U. S. P.

to constant weight  
r cent  
tube determine the  
t of iodine found

corresponds to not less than 51.9 per cent nor more than 52.3 per cent when calculated to the dried substance. Weigh accurately about 0.3 Gm of skiodan in a tared platinum dish, add 5 cc of sulfuric acid, gently heat while the fumes of iodine and sulfur trioxide are evolved, repeat twice, using two portions of 2 cc. of sulfuric acid each time, cool and weigh as sodium sulfate, the percentage of sodium corresponds to not less than 9.3 per cent, nor more than 9.5 per cent calculated to the dried substance.

### WINTHROP CHEMICAL COMPANY, INC.

**Skiodan Powder:** 20 gram bottle.

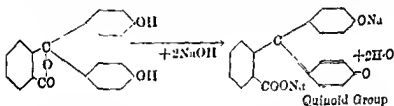
**Sterile Solution Skiodan (40 per Cent by Volume):** 50 cc. bottles.

**Tablets Skiodan:** 1 Gm (for retrograde pycnography)

U. S. patent 1,842,626 (Jan. 26, 1932; expires 1949) U. S. trade mark 283,045

### Phenolphthalein Dyes

Phenolphthalein—long used by chemists as an indicator before its therapeutic properties were discovered—is a condensation product of phthalic anhydride and phenol. In neutral and acid



mediums it exists in a form in which there is no quinoid group but the presence of alkali ( $pH \approx 8$  to 10) causes the characteristic rearrangement with typical salt formation and the presence of a quinoid group whereby the red color is formed.

This reaction is also characteristic of other members of the series. Phenolsulfonphthalein—also used as an indicator—contains an  $SO_2$  group in place of the  $CO$  group in the phthalic anhydride nucleus. In phenoltetrachlorophthalein and phenoltetraiodophthalein the four hydrogen atoms in the benzene ring belonging to the phthalic acid nucleus have been replaced by chlorine and iodine, respectively; in tetrabromophenolphthalein, two bromine atoms are on each phenol group.

**Actions and Uses.**—All of the compounds of the phenolphthalein type are used. phenolphthalein itself action. Phenolsulfonphth

used because they pass unchanged through the body and at the same time have the property of intense color formation when the excretions are collected and alkalinized. Bromsulfalein is used in a somewhat analogous way, but instead of determining the amount excreted by the bile, the amount (not excreted) in the blood gives an index of liver function. Tetrabromophenol-

phthalein and tetraiodophenolphthalein—which are employed in the form of the sodium salts—are used as carriers of bromine or iodine, they appear in the gallbladder in sufficient concentration to permit the heavy halogen atoms to cast a shadow to the roentgen rays

### PHENOLSULFONPHTHALEIN — Phenol Red — U S P

For description and standards see the U S Pharmacopeia under Phenolsulfonphthaleinum and Injectio Phenolsulfonphthaleini

*Actions and Uses*—Solutions of phenolsulfonphthalein injected into the tissues are readily absorbed and are excreted mainly in the urine. A very small amount is excreted in the feces.

Phenolsulfonphthalein is used for determining the functional activity of the kidneys. When injected intramuscularly or intravenously, it begins to be excreted in normal cases in from five to ten minutes. The average normal eliminations after intravenous administration are from 25 to 45 per cent in 15 minutes from 50 to 65 per cent in the first hour, and a total of from 65 to 85 per cent in two hours. Following intramuscular injection 40 to 50 per cent is eliminated in the first hour and from 60 to 75 per cent at the end of two hours. The excretion of the dye is diminished in the presence of cardiac failure, particularly after intramuscular injection.

*Dosage*—One cc of a sterile solution containing 0.006 Gm of phenolsulfonphthalein as the monosodium salt is injected either into the lumbar muscles or into one of the antecubital veins. Great care must be taken that exactly 1 cc is injected.

The original procedure in which the patient was catheterized when the dye was injected and the catheter left in place until the dye was detected in the urine is now seldom followed. From 200 to 400 cc of water should be administered before beginning the test in order to insure free urinary secretion. If the injection is made *intramuscularly* the patient is instructed to void into a receptacle at the end of one hour and ten minutes and into a second receptacle one hour later. If the injection is made *intravenously* the patient is instructed to void into a receptacle at the end of exactly fifteen minutes or at the end of one hour and two hours. Slighter degrees of kidney insufficiency may be detected by a decrease in the amount of dye excreted in fifteen minutes than with longer collection periods.

The urine collected is made alkaline with a 25 per cent solution of sodium hydroxide diluted to 1 liter, and compared with a standard containing 0.006 Gm of alkaline phenolsulfonphthalein per liter.

GEORGE A. BREON & CO. INC.

**Ampul Solution Phenolsulfonphthalein** 1 cc. Each 1 cc of solution contains 6 milligrams of phenolsulfonphthalein in the form of the monosodium salt.



**HYNSON, WESTCOTT & DUNNING, INC.**

**Phenolsulfonphthalein (Powder):** bulk.

**Ampules Solution Phenolsulfonphthalein:** 1 cc. Each 1 cc. of solution contains 6 mg of phenolsulfonphthalein in the form of the monosodium salt.

THE LAKESIDE LABORATORIES, INC.

**Ampul Solution Phenolsulfonphthalein:** 1 cc. Each 1 cc. of solution contains 6 milligrams of phenolsulfonphthalein in the form of monosodium salt.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Phenolsulfonphthalein (Powder):** bulk.

**PHENOLTETRACHLOROPHTHALEIN.**—Phenol-tetrachlorophthaleinum.—A dibasic dye formed by the condensation of phenol and tetrachlorophthalic acid or its anhydride

**Actions and Uses**—Phenoltetrachlorophthalein has been used for the determination of the functional activity of the liver. It can be used, in the form of the sodium salt, intravenously; it should not be given subcutaneously or intramuscularly. It has been proposed that the excretion can be determined by any one of these methods.

1. Its disappearance from the blood stream: S. M. Rosenthal (*J. Pharmacol. & Exper. Therap.* **19**:385 [June] 1922); H. H. Rosenfield and E. F. Schneiders (*J. A. M. A.*, March 17, 1923, p. 743)

2. The excretion of the drug in the duodenum by means of a duodenal tube. Aaron, Beck and Schneider (*J A M A.*, Nov. 19, 1921, p 1631)

3. The excretion of the drug in the stool: Rowntree, Hurwitz and Bloomfield (*Bull. Johns Hopkins Hosp.* 24:327, 1913); Whipple, Peightal and Clark (*Bull. Johns Hopkins Hosp.* 24:343, 1913); Rowntree, Marshall and Chesney (*Proc. Am. 4. Phys. & Surg.* 1914; *J. A. M. A.* 63:1533 [Oct 31] 1914)

**Dosage**—Five milligrams in the form of disodium phenotetrachlorophthalein per Kg. of body weight, intravenously. The solution must not be exposed unduly long, as the salt is sensitive to the action of the carbon dioxide of the atmosphere.

#### Tests and Standards.—

ml. - 4,4'-methylenediphenylthaleim is a cream white powder; odorless; per water; very soluble in the acid; slightly soluble dissolves in solutions of which are deep purple ed on dilution, and in extinction from phenol

ῥητῆραςιν]

Phenoltetrachlorophthalein does not melt when heated to 300 C. It does not respond to the U S P test for heavy metals as described under phenolphthalein.

Dry at 110 C to constant weight.  
 about 5 Gm of sodium hydroxide warm water to to constant weight.  
 matter (tetrachlorofluorane) does not exceed 0.2 per cent. Inesnerate about 2 Gm of the substance accurately weighed the ash does not exceed 0.15 per cent.

## HANSON, WESTCOTT & DUNNING, INC

Phenoltetrachlorophthalein (*Powder*) bulk

**Ampules Solution** Phenoltetrachlorophthalein 2 cc  
 A solution of disodium phenoltetrachlorophthalein each cubic centimeter of which represents 0.05 Gm of phenoltetrachlorophthalein

**PHENTETIOTHALEIN SODIUM** — Sodium Phentetiothaleinas — Phenoltetraiodophthalein Sodium —  $\text{NaOOC}_6\text{H}_4\text{C}_6\text{H}_4\text{OC}_6\text{H}_4\text{ONa}$  The disodium salt of a dye phenoltetraiodophthalein. Phentetiothalein sodium contains from 56 per cent to 59 per cent of iodine.

*Actions and Uses* — Phentetiothalein sodium is used for the

roentgen rays and if the liver is damaged it is retained in the blood in amounts indicative of the extent of impairment. It is claimed to cause little or no toxic reaction. Myocardial insufficiency and uremia are considered contraindications and jaundice enjoins caution.

*Dosage* — Intravenously for visualization of the gallbladder and simultaneous test of liver function 40 mg per kilogram of body weight; the dose need not exceed 2.5 Gm regardless of weight. The dye is dissolved in about an ounce of freshly distilled water, filtered through fine filter paper and sterilized for fifteen minutes in a boiling water bath. The solution should be freshly made not more than twenty-four hours before it is used. It is injected intravenously by gravity with about 150 cc of Ringer's solution in not less than fifteen minutes, either in the morning between 8 and 9 or in the evening between 5 and 9. If given in the evening the evening meal should be omitted and no food given until the first roentgenogram is taken in the morning. At this time a fat meal is given and the roentgenogram taken one hour after the meal and if desired another three hours after the meal to determine the rapidity and char-

acteristics of emptying. More satisfactory results are probably

bladder visualization alone the drug is administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the oral or, if preferred, by the intravenous method. The liver function test cannot be made by this method because the dye is not absorbed rapidly enough into the blood.

To make the determination of liver function, blood is collected one hour after the intravenously administered dye and compared to a set of standard solutions as suggested by Rosenthal (An Improved Method for Using Phenoltetrachlorophthalein as a Liver Function Test, *J. Pharmacol. & Exper. Therap.* 19:385 [June] 1922) and modified by Cole, Copher and Graham (Simultaneous Cholecystography and Determination of Liver Function, *J. A. M. A.* 90:111 [April 7] 1928)

### Tests and Standards—

Phentetiothalein sodium occurs as bronze purple, odorless, slightly hygroscopic granules. It is soluble in water and alcohol.

permanent purple color appears

Intimately mix 0.1 Gm. of the salt with 1.0 Gm. of anhydrous sodium carbonate and heat to fusion; cool the mixture, dissolve in diluted hydrochloric acid and filter, add a few drops of hydrogen peroxide solution and agitate the mixture with a few cubic centimeters of chloroform the chloroform layer is colored violet (iodine)

Transfer about 0.5 Gm., accurately weighed, of phentetiothalein sodium to a flat type weighing bottle and dry in a vacuum at 80 °C to constant weight the loss in weight is not more than 5 per cent

Transfer about 0.3 Gm. accurately weighed, of phentetiothalein sodium to a bomb tube, determine the iodine by the Carious method the amount of iodine found is not less than 56 per cent nor more than 59 per cent when calculated to the dry basis

### IODOPHTHALEIN

Tetraiodophenolphthalein um

—Tetiothalein Sodium—1 um

salt of tetraiodophenolphthalein 85

per cent of tetraiodophenolphthalein The separated tetraiodophenolphthalein contains not less than 60 per cent and not more than 63 per cent of I" U S P

For description and standards see the U. S. Pharmacopeia under Iodophthaleinum Sodicum.

**Actions and Uses**—Iodophthalein sodium is used for the roentgenologic examination of the gallbladder. Following the intravenous injection or, if decomposition is avoided, the oral administration, the substance appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays. After injection, a few of the patients may have unpleasant sensations such as dizziness, nausea, various body pains, and fall in blood pressure. The transitory fall in blood pressure may be relieved by the administration of from 0.5 to 1 cc. of epinephrine hydrochloride solution (1 in 1000) intramuscularly. Iodophthalein sodium is useful as a diagnostic agent, but workers are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses. Myocardial insufficiency and uremia are considered contraindications, and jaundice enjoins caution.

**Dosage**—To visualize the gallbladder in a patient weighing between 115 and 160 pounds (52 and 72.6 Kg.) 3 Gm. of iodophthalein sodium is dissolved in 24 cc., or 3.5 Gm. of iodophthalein sodium is dissolved in 28 cc. of freshly distilled water; the solution is then sterilized by heating the container in boiling water for twenty minutes. For patients weighing over 160 pounds, the maximum dose should not exceed 3.5 Gm. For patients weighing less than 115 pounds (52 Kg.) the amount of salt is to be reduced. The solution is injected intravenously in two doses, one half hour apart, in the morning before breakfast. Care must be taken not to allow extravasation in order to avoid tissue necrosis. Breakfast is omitted. At noon a glass of milk is permitted, and the evening meal is allowed as usual. Water by mouth is allowed at all times.

Iodophthalein sodium may be administered orally. 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each) or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Keratin-coated capsules may be used. Meticulous roentgen technique is necessary, and if the interpretation of the cholecystogram is in question, a control determination should be made either by the oral or, if preferred, by the intravenous method. Iodophthalein sodium is said to be preferable for intravenous injection.

#### ABBOTT LABORATORIES

**Capsules Iodeikon** 0.25 Gm. soluble iodophthalein (keratin-coated)

**Iodeikon Emulsion Powder** Iodophthalein sodium 33.34 per cent in a vehicle composed of malt sugar 37.3 per cent, powdered cocoa 18.3 per cent, tartaric acid 8.25 per cent, vanillin 2.2 per cent, saccharine 0.54 per cent, and menthol 0.07 per cent.

**EASTMAN KODAK COMPANY**

**Tetraiodophenolphthalein Sodium Salt (*Powder*):** bulk.

**THE LAKESIDE LABORATORIES, INC.**

**Ampuls Iodeikon:** 3.5 Gm

**MALLINGRODT CHEMICAL WORKS**

**Iodeikon (*Powder*):** bulk.

**Ampul Iodeikon:** 3.5 Gm. iodophthalein sodium

**MERCK & CO., INC.**

**Iodophthalein Sodium (*Powder*):** 3½ Gm, 25 Gm, 100 Gm, and 500 Gm, bottles

***Toxins for Immunity Tests***

(See under Chapter XXI, Serums and Vaccines, Diagnostic Agents)

***Allergenic Extracts Diagnostic***

(See under Allergenic Preparations.)

## CHAPTER XII

### DIURETICS

#### Mercury Compounds

**MERCUROPHYLLINE INJECTION** — A sterile solution in water for injection of the sodium salt of *B* methoxy  $\gamma$  hydroxymercuri propylamide of trimethyl cyclopentane dicarboxylic acid ( $C_{14}H_{19}NO_5HgNa$ ) (the mercuri compound) and of theophylline in approximately molecular proportions. It contains an amount of mercury equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of the mercuri compound and not less than 93 per cent and not more than 107 per cent of the labeled amount of theophylline ( $C_7H_8N_4O_2 \cdot H_2O$ ) *U S P*

For description and standards see the *U S Pharmacopeia* under *Injectio Mercuriophyllinae*

*Actions and Uses* — Mercuriophylline injection is a potent diuretic. It is perhaps less toxic and more active than the purine free mercurial diuretics. It has been demonstrated that when theophylline is combined with the mercurial sloughs and venous thrombosis occur with less frequency and severity. Clinical experiments suggested that the presence of theophylline enhances the rate and completeness of absorption so that the drug is effective and well tolerated by intramuscular as well as intravenous administration. Studies by a number of investigators give indication that mercuriophylline injection is an efficient diuretic. Supplementary administration of acidic salts such as ammonium chloride tends to increase the diuresis.

Mercuriophylline injection is used to remove excess fluid in edema of congestive heart failure, nephrosis and cirrhosis of

depletion

*Dosage* — Intramuscularly an amount equivalent to 0.1 Gm. of the mercuri compound and 40 mg. of theophylline. Care should be taken to prevent leakage into the subcutaneous tissue. If it is desired to determine if the patient may have intolerance to the compound a much smaller dose should be injected for trial. Mercuriophylline injection is supplied in a concentration of 10 per cent (weight/volume) with respect to the sodium salt of the mercurated organic acid and 3.53 per cent with respect to anhydrous theophylline. Each cubic centimeter of mercuriophylline injection represents 39 mg. of mercury in non-ionizable form.

## CAMPBELL PRODUCTS, INC.

Ampoules Mercupurin: 1 cc. and 2 cc.

U. S. patents 2,116,872 (May 10, 1938; expires 1955); 2,117,901 (May 17, 1938, expires 1955). U. S. trademark 315,683.

**MERSALYL AND THEOPHYLLINE.**—A mixture containing two parts by weight of mersalyl U. S. P. and one part by weight of theophylline U. S. P.

*Actions and Uses.*—(See under Mersalyl and Theophylline Injection.)

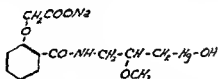
*Dosage.*—Two tablets may be given in one dose in the morning after breakfast and repeated in four to five days if required. As an adjunct to intravenous medication, one tablet may be given daily for one or two weeks but in such instances rest periods of one or two weeks should intervene between courses of treatment.

## WINTHROP CHEMICAL COMPANY, INC.

**Salyrgan-Theophylline Enteric Tablets:** Each tablet contains 0.08 Gm. mersalyl and 0.04 Gm. theophylline and is coated with shellac.

**MERSALYL AND THEOPHYLLINE INJECTION.**

—Mersalyl and Theophylline Ampuls.—"A sterile solution in water for injection of approximately 10 parts by weight of mersalyl ( $C_{12}H_{14}HgNO_2Na$ ) to each 5 parts by weight of theophylline ( $C_7H_8N_4O_2 \cdot H_2O$ ). It contains mercury (Hg) equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of mersalyl, and not less than 93 per cent and not more than 107 per cent of the labeled amount of theophylline." U. S. P.



For description and standards see the U. S. Pharmacopoeia under *Injectio Mersalytis et Theophyllinae*.

*Actions and Uses.*—Mersalyl and theophylline injection has been demonstrated to produce less local reaction on intramuscular injection than mersalyl alone and to be somewhat more effective. It is believed that the more rapid resorption of mersalyl in combination with theophylline accelerates diuresis and, by preventing the deposition of mercury, improves the local tolerance. Mersalyl and theophylline injection is proposed as a diuretic for dropsy in cardiorenal disease and in nephrosis, ascites of liver diseases and other conditions. It is contraindicated in acute nephritis and chronic kidney disease in an advanced stage with marked tubular and glomerular changes, also intestinal inflammation with diarrhea. As do other mer-

curials mersalyl and theophylline injection may give rise to side effects particularly stomatitis gastric disturbance, more or less diarrhea vertigo, headache febrile reaction and cutaneous eruptions. When the use of mersalyl and theophylline injection is continued over a prolonged period of time the urine should be examined from time to time for albumin casts and blood cells. Sudden fatalities have been reported following the use of mercurial diuretics and while these mishaps are rare compared to the number of times these drugs are used caution should be exercised. Since the available evidence is in favor of ventricular arrhythmia as the mechanism of these fatalities, especial precautions should be exercised in patients who already are candidates for such arrhythmia, for example, patients with frequent ventricular beats heavily digitalized patients or those with recent myocardial infarction.

**Dosage**—For Adults Intramuscularly mersalyl 0.2 Gm and theophylline 0.1 Gm. For susceptibility test the patient with one half of the recommended dose. If well tolerated the recommended dose may be given on the following day. In some cases this may have to be doubled for the full effect. Usually injections are not given more frequently than every three or four days. After relief of the dropsy recurrences can often be prevented by occasional injections. For Children The above recommendations should be reduced by one half.

#### WINTHROP CHEMICAL COMPANY, INC

##### Salyrgan-Theophylline Solution

**Ampoules Solution Salyrgan-Theophylline** 1 cc and 2 cc. Each cubic centimeter contains mersalyl 0.1 Gm and theophylline 0.05 Gm.

U. S. patent 1,693,432 (Nov. 27, 1928 exp. res. 1945) U. S. trade mark 288,515

#### Urea

**UREA**—Carbamide— $\text{CH}_4\text{N}_2\text{O}$ —U. S. P.

For description and standards see the U. S. Pharmacopoeia under Urea.

**Actions and Uses**—Urea is an active diuretic; it is rapidly eliminated and is not poisonous. It is useless in the treatment of tuberculosis and has no important solvent action on urinary calculi. It may be employed when diuresis is indicated though it appears irrational in any renal disease characterized by retention of nitrogen. Urea should not be used as a diuretic when there is impaired elimination. Concentrated solutions of urea dissolve protein readily, but have little action on healthy tissue; hence urea has been used for the removal of necrotic tissue in infected wounds and for the removal of foul odors. Certain observers believe that even weak solutions stimulate granulation and hasten the healing of wounds.

**Dosage**—From 0.5 to 4 Gm. Urea is given in solution or it may be enclosed in cachets.



## MALLINCKRODT CHEMICAL WORKS

Urea Pure Crystals: bulk.

MERCK &amp; CO., INC.

Urea (Crystals): bulk.

## Xanthine Derivatives

*Structure and Relations*—Caffeine, theobromine and theophylline are methyl xanthines, derived from xanthine by the introduction of two or three methyl radicals into a corresponding number of  $\text{NH}_2$  groups. As these may occupy various positions in the xanthine nucleus, a considerable number of methyl xanthines exist, naturally or by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance, namely, caffeine (1:3:7 trimethylxanthine); theobromine (3:7 dimethylxanthine), and theophylline (1:3 dimethylxanthine).

Caffeine is usually obtained from tea or coffee; theobromine is obtained from cacao, or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available. It is prepared synthetically. Theocln is a proprietary name for synthetic theophylline.

*Actions and Uses*.—Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally, or more, effective, more prompt, and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds true, particularly for theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting; it may produce gastric disturbances; renal irritation has been reported. Theobromine is, therefore, generally preferred, sometimes preceded for a few days by theophylline. If central stimulation is desired, caffeine must be used. In recent years the xanthine derivatives have been used but seldom as diuretics as a result of the introduction of the more effective mercurial diuretics.

*Compounds*.—The slight solubility of theobromine and theophylline limits their usefulness exclusively in the form of the <sup>and almost</sup> as theobromine with sodium form with a considerable number of compounds. There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various preparations which have been introduced are strictly equivalent.

*Theobromine Compounds*

**THEOBROMINE AND SODIUM ACETATE**—A hydrated mixture of theobromine sodium ( $C_7H_7N_4O_2Na$ ) and sodium acetate ( $NaC_2H_3O_2$ ) in approximately molecular proportions. It yields not less than 55 per cent and not more than 65 per cent of theobromine ( $C_7H_7N_4O_2$ ). U S P

For description and standards see the U S Pharmacopoeia under Theobromina et Sodii Acetas.

*Actions and Uses*—The uses of theobromine are similar to those of caffeine but its action is said to be relatively greater on the heart and muscles and also as a diuretic. It does not act so powerfully on the central nervous system.

Theobromine sodium acetate acts like theobromine over which it has the advantages of greater solubility and of being well tolerated by the stomach. While inferior in diuretic power to theophylline (which see) it is said to have greater power in sustaining the diuresis produced.

*Dosage*—From 0.5 to 1 Gm preferably in wafers or capsules. If in solution this should be freshly prepared (with peppermint water) without sugar or mucilage.

**MAILLONBROT (CHEMICAL WORKS)**

**Theobromine and Sodium Acetate (Powder)** bulk

Merck & Co., Inc.

**Theobromine and Sodium Acetate (Powder)** bulk

**THE SMITH DORSEY COMPANY**

**Tablets Theobromine with Sodium Acetate** 0.5 Gm (77 grains)

**THEOCALCIN**—A double salt or mixture of calcium theobromine ( $[C_7H_7O_2N_4]_2Ca$ ) and calcium salicylate ( $[C_7H_5O_3]_2Ca$ ). It contains not less than 44 per cent of theobromine.

*Actions and Uses*—Theocalcin acts like theobromine, over which it has the advantage of greater solubility. It is however less soluble than theobromine with sodium salicylate on this account it is claimed to be less likely to produce gastric irritation.

*Dosage*—Average dose from 0.5 to 1 Gm three times a day.

*Tests and Standards*

Theocalcin is a white amorphous powder having a saline taste. It is readily soluble in water.

precipitate forms which dissolves on addition of a few drops of hydrochloric acid. To about 0.03 Gm of the precipitate obtained in



**THEOPHYLLINE ETHYLENEDIAMINE**—U S P  
—Aminophylline—"Contains not less than 75 per cent and not more than 82 per cent of anhydrous theophylline ( $C_7H_8N_4O_2$ ) and not less than 123 per cent and not more than 138 per cent of ethylenediamine ( $C_2H_4(NH_2)_2$ )." U S P

For description and standards see the U S Pharmacopeia under Theophyllina Aethylenediaminica, Injectio Theophyllinae Aethylenediaminicae and Tabellae Theophyllinae Aethylene diaminicae

*Actions and Uses*—Theophylline ethylenediamine has the actions and uses of theophylline and theophylline with sodium acetate, over which it has the advantage of greater solubility. Like these it has a diuretic action and the xanthine derivatives are useful diuretics in congestive heart failure. There is apparently no satisfactory evidence to show that these drugs exert an immediate action which justifies their use in acute pulmonary congestion or edema, although they may be useful in preventing attacks by their diuretic effects. The xanthines stimulate the myocardium to increased vigor of contraction. This is accompanied by increased cardiac output and increased work of the heart. Clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory, and claims for such use do not appear acceptable in view of the existing evidence. Increased coronary blood flow produced by theophylline in the experimental animal follows, rather than precedes, the myocardial stimulation and claims for the clinical use of this drug in increasing the blood supply to the heart are not acceptable until it can be shown that the increase in coronary flow is disproportionately large in comparison to the increase in cardiac metabolism. The xanthines are useful in the treatment of Cheyne Stokes respiration. At times the effect is transient but in other cases the effect may last several hours. Aminophylline is effective in the treatment of bronchial asthma, it finds its greatest field of usefulness in patients who have become epinephrine fast. It is probably a safer drug than epinephrine in occasional cases where there may be indecision concerning the bronchial or 'cardiac' nature of asthmatic attacks. In general it is less effective than epinephrine and should not supplant the latter. There is no basis for claims that the xanthines effectively reduce high blood pressure. The available evidence is opposed to claims that these drugs are useful in the treatment of peripheral vascular disease.

*Dosage*—Orally, from 0.1 to 0.2 Gm three times daily may be necessary but it is pointed out that this high dosage is warranted only in exceptional cases, by rectal administration.

**AMERICAN PHARMACEUTICAL Co., INC.**

Tablets Aminophylline: 0.1 Gm. and 0.195 Gm.

**ERNST BISCHOFF Co., INC.**

Aminophyllin (*Powder*): bulk

Tablets Aminophyllin: 0.1 Gm.

**H. E. DUBIN LABORATORIES, INC.**

Ampules Solution Aminophyllin: 0.24 Gm in 10 cc.

Ampules Solution Aminophyllin: 0.48 Gm. in 2 cc.

Ampules Solution Aminophyllin: 0.48 Gm. in 20 cc.

Suppositories Aminophyllin: 0.36 Gm

Tablets Aminophyllin: 0.1 Gm

Tablets Aminophyllin: 0.2 Gm.

Tablets Aminophyllin: 0.2 Gm. (enteric coated).

**ENDO PRODUCTS, INC.**

Tablets Aminophyllin: 0.1 Gm

Ampule Solution Aminophylline: 0.48 Gm in 2 cc.

Ampule Solution Aminophylline: 0.24 Gm in 10 cc

**GANE AND INGRAM, INC.**

Aminophylline (*Powder*): bulk

**THE LAKESIDE LABORATORIES, INC.**

Ampules Solution Aminophylline: 0.48 Gm. in 2 cc

Ampules Solution Aminophylline: 0.24 Gm in 10 cc.

Ampules Solution Aminophylline: 0.48 Gm in 20 cc

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm

Tablets Aminophyllin: 0.2 Gm., enteric coated

**LEDERLE LABORATORIES, INC.**

Ampuls Solution Aminophyllin: 0.24 Gm. in 10 cc

Ampuls Solution Aminophyllin: 0.48 Gm. in 2 cc

Tablets Aminophyllin: 0.1 Gm. and 0.2 Gm

**THE WM. S. MERRELL COMPANY**

Ampul Solution Aminophylline: 0.48 Gm in 2 cc

Ampul Solution Aminophylline: 0.24 Gm in 10 cc

Aminophylline Tablets: 0.1 Gm

**E. S. MILLER LABORATORIES, INC.**

Theophylline Ethylenediamine Injection, 2.4% W/V:  
10 cc and 20 cc ampuls.

Ampul Solution Aminophylline 24% W/V in Ethylene diamine Solution 1% V/V (with Benzyl Alcohol 2% V/V) 2 cc.

Tablets Theophylline Ethylenediamine 0.1 Gm and 0.2 Gm

#### PHARMEDIC CORPORATION

Aminophylline (*Powder*) bulk

Ampule Solution Aminophylline 0.24 Gm in 10 cc

Ampule Solution Aminophylline 0.48 Gm in 2 cc

Suppositories Aminophylline 0.36 Gm

Tablets Aminophylline 0.1 Gm

#### G. D. SEARLE & CO

Aminophyllin (*Powder*) bulk

Ampules Solution Aminophyllin 0.24 Gm in 10 cc

Ampules Solution Aminophyllin 0.48 Gm in 2 cc with benzyl alcohol 0.04 Gm in sufficient distilled water to make 2 cc

Ampules Solution Aminophyllin 0.48 Gm in 20 cc

Tablets Aminophyllin 0.1 Gm and 0.2 Gm

Tablets Aminophyllin 0.2 Gm Enteric Coated The enteric coating consists of a mixture of mastic and magnesium stearate

#### THE SMITH DORSEY COMPANY

Ampoule Solution Aminophylline 0.5 Gm in 20 cc

Ampoule Solution Aminophyllin 0.25 Gm in 10 cc

Ampoule Solution Aminophyllin 0.5 Gm in 2 cc

Tablets Aminophyllin 0.1 Gm and 0.2 Gm

#### THE WARREN TEED PRODUCTS COMPANY

Tablets Aminophylline 0.1 Gm

#### THEOPHYLLINE AND SODIUM ACETATE—

U. S. P.—Theocin Soluble—Yields not less than 55 per cent and not more than 65 per cent of anhydrous theophylline ( $C_7H_8N_4O_2$ ) U. S. P.

For description and standards see the U. S. Pharmacopoeia under Theophyllina et Sodii Acetas and Tabellae Theophyllina et Sodii Acetatis

*Dosage*—From 0.2 to 0.35 Gm best given after meals

#### WINTHROP CHEMICAL COMPANY INC

Theocin Soluble (*Powder*) bulk

Tablets Theocin Soluble 0.16 Gm

U. S. Patent 716,994 (Dec. 30, 1902) exp. ed. U. S. trademark

## CHAPTER XIII

### ECBOLICS

Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition, a great variety of chemical substances have been isolated from the crude drug. These include carbohydrates, lipoids, dyes, amino acids, and a number of biogenous amines. Of the last group may be mentioned histamine, tyramine, and acetylcholine, substances which are pharmacologically active but which play a negligible role in the therapeutic effect of the drug.

The alkaloids thus far isolated consist of several pairs of optical isomers, one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

Potent	Relatively Inactive	Formula
1. Ergotoxine	Ergotinine $\psi$ Ergotinine	$C_{26}H_{33}O_5N_3$
2. Ergotamine	Ergotaminine	$C_{26}H_{33}O_5N_3$
3. Ergosine	Ergosinine	$C_{26}H_{33}O_5N_3$
4. Ergocristine	Ergocristinine	$C_{26}H_{33}O_5N_3$
5. Ergonovine	Ergometrinine	$C_{26}H_{33}O_5N_3$

It may be noted that the first of the five groups consists of three rather than of two members, and furthermore that the ergotoxine and ergocristine groups are isomeric with each other. It is also striking that the molecular size of ergonovine is definitely less than that of the other alkaloids. The inert alkaloids in solution in chloroform show a high degree of dextro-rotation, while the active alkaloids are levorotatory, ergonovine showing a much smaller degree of levorotation than the others.

Various molecular complexes consisting of a potent and an inert alkaloid have also been isolated. These may show a pharmacologic activity somewhat different from the average of those of its components. In this group may be mentioned sensibamine (ergotamine plus ergotaminine) and ergoclavine (ergosine plus ergosinine).

Common to all of the above alkaloids is a hydrolysis product, lysergic acid ( $C_{26}H_{33}O_5N_3$ ), which contains an indole group (Ergomonamine,  $C_{26}H_{33}O_5N_3$ , an alkaloid recently isolated from ergot and the pharmacology of which is still unknown, lacks this characteristic chemical group.) Isomerism in the lysergic acid part of the molecule is believed to account for differences in members of the same pair. The various pairs of alkaloids differ in the other products of hydrolysis, which are unique in the field of alkaloidal chemistry in that certain of them are

amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs e. g. ergotoxine and ergonovine.

Ergotoxine may be crystallized from benzene, carbon bisulfide and acetone. It is insoluble in water and light petroleum, sparingly soluble in ether and very soluble in methyl and ethyl alcohol, chloroform, acetone and ethyl acetate. The phosphate of ergotoxine is soluble in 313 parts of water at room temperature, the ethanesulfonate is sparingly soluble in water, somewhat more soluble in ethyl alcohol and dissolves readily in methyl alcohol. Ergotamine is insoluble in water, sparingly soluble in ethyl alcohol and very readily soluble in chloroform.

Ergotamine is readily soluble in ethyl alcohol, soluble in water, is readily hydrolyzed to ergotamine phosphate, all soluble in water, in pyridine. It is much less soluble than ergotamine in other solvents from which it crystallizes relatively solvent free, unlike most of the ergot alkaloids which tend to retain solvent of crystallization.

Ergonovine may be crystallized from a number of solvents, possibly most readily from benzene and chloroform. In contrast to the other alkaloids it is appreciably soluble in water and comparatively insoluble in chloroform. It forms many crystalline salts which are markedly soluble in water. Ergonovine is more basic than the other alkaloids and less readily precipitated by Mayer's reagent. It is present in aqueous and alcoholic extracts of those ergots which contain it, unlike ergotoxine and ergotamine which are extracted by alcohol but not by water. The content of ergonovine is not constant in specimens of ergot from different localities and may even vary in specimens from the same locality. It occurs in lower concentrations (up to 0.2 mg. per Gm. of ergot) than does the ergotoxine-ergotamine group which may reach 2 mg. per Gm. of ergot. Ergometrine is even more basic than ergonovine, much more soluble in chloroform, only slightly soluble in water and may be crystallized from acetone. It forms crystalline salts unlike the other alkaloids of the inert series.

*Pharmacology*.—Ergotoxine, ergotamine, ergosine and presumably ergocristine show essentially the same type of pharmacologic action although certain individual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic contractions of the uterus. The blood pressure is increased through peripheral stimulation of the motor sympathetic mechanism and also a paralysis of this mechanism is produced so that the effect of epinephrine on the blood pressure is lessened or reversed. The inhibition of epinephrine action



by ergot alkaloids may also be demonstrated on other smooth muscle organs, more readily on those to which the sympathetic nerve supply is predominantly motor, such as the rabbit uterus. In sufficient dosage they cause cyanosis of the cockscomb and with toxic doses gangrene through vascular occlusion. Gangrene may also appear clinically on administration of toxic doses. The vascular effects of these alkaloids vary considerably both in animals and in man. Poisonous doses in the intact animal produce acute manifestations essentially due to central action consisting of excitement, tremor, weakness, pyrexia, vomiting, convulsions, and certain signs of sympathetic stimulation.

Ergotoxine shows slightly greater activity than ergotamine in inhibiting the action of epinephrine on isolated tissues. Ergosine is probably even more potent than ergotoxine in this regard. Ergotamine is only about two-thirds as toxic to white mice as ergotoxine, and the latter alkaloid is at least twice as effective on body temperature as ergotamine, small doses causing a fall and larger doses a rise in temperature by action on the central nervous system.

Ergonovine is effective on the uterus in smaller doses and concentrations than are the other alkaloids. This difference is particularly apparent in the puerperal state when the uterus is especially sensitive to ergonovine. The uterine action is the only appreciable effect of moderate doses of ergonovine, unpleasant side actions being rarely encountered clinically. The promptness of the uterine action, in comparison with that produced by ergotoxine and ergotamine, is an outstanding clinical feature; also it is much more effective when administered by mouth than are the latter alkaloids. It increases both the tone and the rate and amplitude of rhythmic contractions of the uterus, the latter effects probably being proportionately greater than the tonus changes. The duration of effect, although probably less than that of ergotoxine and ergotamine, is at least comparable with that of these alkaloids. The circulatory effects which are referable to actions on the central nervous system and peripheral vascular mechanism vary with the animal and with experimental conditions. A slight increase in blood pressure may be encountered clinically. Ergonovine shows a definite sympathomimetic effect and little or no inhibition of epinephrine action. Although it produces the characteristic cockscomb reaction, it shows definitely less tendency to produce gangrene than ergotoxine and ergotamine. It is less toxic than these two alkaloids, but in poisonous doses produces similar effects.

*Assay*—All ergot preparations, especially those containing water, deteriorate with age. It is necessary therefore to standardize them, and the date of assay should be indicated on the container.

Ergot is assayed officially in this country by the cockscomb method (see U. S. P. XII), which measures the total pharmacologically active alkaloids. Various physical and chemical methods which measure the total alkaloidal content have also been employed. Of this group, the colorimetric method, which

utilizes the blue coloration produced by p dimethylaminobenzal dehyde with the alkaloids and dependent on the indole group of the lysergic acid component, has been extensively used. Such methods do not distinguish between ergonovine and the ergotoxine-ergotamine group, and consequently are not a true measure of the pharmacologic potency unless a constant proportion of these groups in various ergots could be assumed. To overcome this difficulty, assays involving a previous separation of the two groups have been proposed. The Broom Clark method, which is based on the inhibition of the action of epinephrine on the isolated rabbit uterus, does not assay ergonovine, which lacks this particular action.

**ERGOT.**—Ergot of Rye — *Secale Cornutum* P. I. — "The dried sclerotium of *Claviceps purpurea* (Fries) Tulasne (Fam. *Hypocreaceae*), developed on rye plants.

"The potency of Ergot shall be such that when assayed as directed, 1 Gm. shall be equivalent to not less than 0.5 milligram of the U. S. P. Ergotoxine Ethanesulfonate Reference Standard." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Ergota* and *Fluidextractum Ergotae*.

**Actions and Uses.**—The several active principles of ergot have actions that differ somewhat, and the combined effect is utilized in ergot. The action of histamine and tyramine in ergot is probably negligible, and only the alkaloids exert a prolonged effect on the human uterus when ergot is used clinically.

Ergot causes powerful tone, sometimes tetanic contractions of the uterus. It also produces contractions of other involuntary muscles such as those of the blood vessels, bladder, stomach and intestines. Extreme and long continued contraction of the blood vessels, especially of those of the extremities, may lead to gangrene.

The principal use of ergot is to prevent postpartum hemorrhage. For this purpose a full dose is sometimes given as soon as the second stage of labor terminates, but it should not be given until the placenta has been expelled. Its use during labor should be avoided, as it may cause rupture of the uterus or asphyxia of the child. It is employed as a prophylactic for "after pains." Ergot is also used for hemorrhage from the uterus in menorrhagia and metrorrhagia. Its use for hemorrhage from other internal organs is not rational.

Ergot has also been employed in a number of other conditions, in which, however, it is not recommended. These include congestions in various regions, early stage of acute pneumonia, pulmonary congestion, in typhoid fever, diabetes insipidus, colliquative night sweats due to relaxation of the blood vessels and circulatory failure.

**Dose.**—2 Gm. It is sometimes administered in the form of powder, but most commonly in the form of fluid extract.

**ERGOT ASEPTIC.**—A liquid extract of ergot, standardized by the cockscomb method of assay to have the same potency as fluidextract of ergot-U. S. P.

*Actions and Uses.*—The same as those of ergot.

*Dosage.*—1 to 2 cc. Ergot aseptic is intended for intramuscular injection. Ergot aseptic is marketed in ampules only. The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture.

*Preparation.*—

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid. The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C. A large excess of alcohol is added to the concentrated percolate and the material which precipitates is removed. The liquid portion is freed from alcohol by distillation in a partial vacuum at a low temperature, and chlorobutanol in the proportion of 0.005 Gm. per cc. added to the aqueous slightly acid liquid. After three weeks the liquid is assayed, adjusted to proper volume and sealed in ampules. The finished ampules are tested for sterility and potency.

Ergot aseptic is standardized to the same potency as fluidextract of ergot U. S. P., as determined by the cockscomb method described in the U. S. P.

PARKE, DAVIS & COMPANY

Ampoule Ergot Aseptic: 1 cc

**ERGOTAMINE TARTRATE.**— $(C_{12}H_{15}N_2O_5)_2 \cdot H_2C_4H_4O_6$ .  
—"The tartrate of an alkaloid obtained from ergot." U. S. P.

For description and standards see the U. S. Pharmacopeia under Ergotaminae Tartras and Tabellae Ergotaminae Tartratis

*Actions and Uses.*—Ergotamine tartrate stimulates the motor nerve endings of the sympathetic division of the autonomic nervous system, thus causing an increase in blood pressure, contraction of the uterus, etc. (the isolated uterus of the guinea pig is affected in dilutions of from 1 in 150,000,000 to 1 in 200,000,000). In large doses it paralyzes the sympathetic nerve endings. It causes the darkening of the cockscomb characteristic of the action of ergot and in toxic doses causes gangrene and convulsions. There is evidence that ergotamine tartrate is of value in many cases of migraine. The drug is not always a prophylactic and its continued administration will not always prevent attacks. Caution in its use is advisable on account of the danger of poisoning from long continued use or overdosage.

Ergotamine tartrate is proposed for use when the action of ergot to produce uterine contraction is desired; it is contraindicated whenever tonic contraction of the uterus would be dangerous. Ergotamine tartrate is also stated to be indicated in hemorrhage following abortion, after curettage and in postpartum endometritis. It is also used by some physicians in conditions in which there is believed to be overactivity of the sympathetic nervous system, but its value here is not established.

*Dosage* — Intramuscularly, the average dose is 0.25 mg orally, 1 mg two to four times daily. Caution should be exercised in the repeated use of ergotamine, cases of gangrene have been reported where the use of the alkaloid has been continued over a period of some days. For migraine the dose recommended is 0.25 mg by subcutaneous injection to be followed in two or three hours by a full dose of 0.5 mg if no untoward effects have been seen or if the original dose has not been effective. If preferred two or three tablets containing 1 mg each may be given sublingually or by ingestion to be repeated hourly up to 8 or 9 tablets but this method of administration is not so effective as when the drug is given by the subcutaneous route.

**SANDOZ CHEMICAL WORKS INC**

**Ampule Solution Gynergen** 0.5 cc and 1 cc. Each cc contains 0.5 mg of ergotamine tartrate and a small excess of tartaric acid.

**Gynergen Solution** 15 cc and 100 cc bottles. Each cc contains 1 mg of ergotamine tartrate and a small excess of tartaric acid.

**Tablets Gynergen** 1 mg

U S patent 1,394,233 (Oct 18, 1921, expired 1938) 1,435,187 (Nov 14, 1922, expired 1939) U S trademark 173,047

## CHAPTER XIV

### GASTROINTESTINAL DRUGS

#### Antacids

**ALUMINUM HYDROXIDE GEL-N. N. R.**—An aqueous suspension containing not less than 3 per cent nor more than 4.2 per cent of aluminum oxide, chiefly in the form of aluminum. Flavoring, sweetening and preservatives may be added.

See also standards of the U. S. Pharmacopeia under *Gelatum Aluminium Hydroxidi*

*Actions and Uses.*—Aluminum hydroxide gel has been shown to be an effective gastric antacid and neutralizes hydrochloric acid of the stomach by chemical reaction. It does not increase the  $pH$  of the gastric juice beyond the point which interferes with peptic digestion, does not stimulate a compensatory increase in free gastric acidity and does not produce systemic alkalization, which are the principal disadvantages of ordinary alkalis. The amphoteric nature of aluminum hydroxide gel is not of clinical significance because it reacts as an acid only in fluids with a  $pH$  above 9; such a  $pH$  is not encountered in the gastrointestinal tract. Its so-called buffer action occurs only at a  $pH$  of about 4. It is presumed that the acid salt aluminum chloride, which is formed by the reaction of aluminum hydroxide with hydrochloric acid in the stomach, is reconverted to the original compound or other aluminum compounds by reaction with the less acid contents of the small intestine, and the chloride is reabsorbed. Its mild astringent and demulcent properties are believed to be of some importance in the local effect on peptic ulcer. Some evidence also suggests that its effectiveness may be further explained by the tendency to increase mucin secretion and the ability to precipitate pepsin *in vitro*.

As with other aluminum compounds, aluminum hydroxide is not absorbed from the gastrointestinal tract to any appreciable extent and is therefore nontoxic when administered orally. Its astringent property may produce a constipating effect.

There is evidence available to suggest that administration of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency in the presence of a relative or absolute pancreatic deficiency, diarrhea or low phosphorus diet by combination with phosphates in the intestinal tract. This objection does not affect its usefulness in uncomplicated peptic ulcer and gastric hyperacidity, since the diet employed in these conditions is ordinarily relatively rich in phosphorus. Aluminum hydroxide gel may possess adsorptive properties, but specific conclusive evi-

dence that acid, toxins, bacteria or gases are absorbed is lacking, and in the case of hydrochloric acid is opposed by *in vitro* evidence to demonstrate that its reaction with this substance is completely accounted for on the basis of simple chemical neutralization.

Aluminum hydroxide gel is recognized for oral use as an adjunct in the treatment of peptic ulcer (gastric and duodenal) to promote healing, relieve pain and control hemorrhage in this condition and for the control of symptomatic gastric hyperacidity only. Its oral or rectal use in the treatment of other gastrointestinal conditions is not adequately supported by existing clinical evidence.

**Dosage**—Aluminum hydroxide gel is administered orally in doses of from 4 to 8 cc in one-half glass of water or milk every two or four hours, or one-half to one hour after meals. It may be administered by the method of continuous drip by stomach tube in dilutions of 1 part to 2 or 3 parts of water (25 to 33½ per cent aluminum hydroxide gel) at the rate of 15 to 20 drops a minute for a total of approximately 1,500 cc of diluted suspension per twenty-four hours.

#### Tests and Standards—

Aluminum hydroxide gel occurs as a white or light gray suspension which may settle out to some extent or form a semisolid on standing but which liquefies on shaking. The specific gravity at 25° C is from 1.030 to 1.042.

Transfer about 5 Gm of aluminum hydroxide gel to a glass con-

Dissolve 10 Gm of aluminum hydroxide gel in 10 cc of diluted hydrochloric acid and boil. Cool, dilute to 250 cc and filter if necessary. To 10 cc add 1 cc of barium chloride solution and allow to stand for ten minutes. The turbidity is not greater than that produced by 0.2 cc of fiftieth normal sulfuric acid in 10 cc of water.

The pH at 25° C of aluminum hydroxide gel is between 6.4 and 7.2. Dissolve 2.5 Gm of the gel in 5 cc of diluted sulfuric acid and boil. The solution meets the U S P XI test for arsenic. Dissolve 10 Gm of aluminum hydroxide gel in 10 cc of diluted sulfuric acid. The resultant solution conforms to the U S P XI test for heavy metals.

Transfer 25 Gm of an Erlenmeyer flask, potassium chromate so to a faint pink color cent

Transfer also to an Erlenmeyer flask with tenth normal acid in 0.5 cc blue as in less than 2,500 cc

Transfer a to a 250 cc chloride acid red with am four times 1

ately weighed diluted hydro- fine to methyl sing and wash spitate free of

chlorides with an aqueous solution containing 1 part of ammonia water in 25 parts of solution. Dry the precipitate and ignite at 900 C. to constant weight; the aluminum oxide content is not less than 3 nor more than 4.2 per cent.

### WINTHIROP CHEMICAL COMPANY, INC.

**Creamalin:** Contains 55 per cent aluminum hydroxide (equivalent to 36 per cent aluminum oxide). Oil of peppermint is added as a flavoring agent. Marketed in bottles of 180, 240, 360 and 480 cc.

**Creamalin (Unflavored):** Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Marketed in bottles of 180 cc and 480 cc.

### MACALLISTER LABORATORY

**Aluminum Hydroxide Gel:** 480 cc. and 384 liter bottles. Contains 46 per cent aluminum hydroxide (equivalent to 30 per cent aluminum oxide) with saccharin-U. S. P. and oil of peppermint-U. S. P. as flavoring agents.

### SCHIEFFELIN & Co.

**Aluminum Hydroxide Gel:** Contains 55 per cent aluminum hydroxide (equivalent to 36 per cent aluminum oxide). Saccharin and Oil of Peppermint U. S. P. are added as flavoring agents. Marketed in bottles of 480 cc and 384 liters.

**ALUMINUM PHOSPHATE GEL.**—An aqueous suspension containing not less than 38 per cent nor more than 42 per cent of aluminum phosphate ( $AlPO_4$ ). Flavoring, sweetening and preservatives may be added.

**Actions and Uses.**—Aluminum phosphate gel has antacid, . . . . .  
 . . . . . orp-  
 . . . . . hate

gel is less than one half that of aluminum hydroxide gel of the same concentration, claims that it possesses advantages over the latter preparation in the treatment of peptic ulcer are not permissible except when the ulcer is associated with a relative or absolute deficiency of pancreatic juice, diarrhea or low phosphorus diet. The evidence indicates that, despite its lower combining power, aluminum phosphate gel therapy gives as good results in the treatment of peptic ulcer, but for the present its use should be restricted to patients under conditions or with complications likely to produce phosphorus deficiency.

**Dosage.**—Fifteen to 30 cc. alone or with water or milk may be administered every two hours during the active stage of the ulcer. Later the dose may be reduced to 45 cc. four times daily (with or after each meal and at bedtime) or to 30 cc. six times daily (with or after and between meals and at bedtime).

*Tests and Standards—*

Aluminum phosphate gel occurs as a white odorless suspension which may settle out to some extent on standing. Its specific gravity at 25 C is from 1.032 to 1.044. The pH at 25 C of aluminum phosphate gel is between 6.0 and 7.2.

Dilute 1 Gm of aluminum phosphate gel to 100 cc and mix. To 5 cc of the diluted gel add 1 cc of sodium hydroxide solution (1 cc of 1 per cent alcoholic alizarin sulfonate solution and neutralize with 36 per cent acetic acid).  
 5 cc portion of the  
 2 cc of ammonium  
 which dissolves in it  
 solution. Add 30 cc  
 aluminum phosphate  
 pH of the mixture is

another  
 acid and  
 appears  
 colorless  
 Gm of  
 uses the

Transfer 5 Gm of aluminum phosphate gel to a glass container add 10 cc of diluted hydrochloric acid and agitate the mixture yields a clear and colorless solution within ten minutes to this solution add 8 cc of ammonia water a flocculent precipitate appears which is insoluble in excess ammonia water but soluble in sodium hydroxide solution.

Dissolve 10 Gm of aluminum phosphate gel in 10 cc of diluted hydrochloric acid and boil. Cool dilute to 250 cc and filter if necessary. To 10 cc add 1 cc of barium chloride solution and allow to stand for ten minutes the turbidity is not greater than that produced by 0.2 cc of fifth normal sulfuric acid in 10 cc of water. Dissolve 2.5 Gm of the gel in 5 cc of diluted sulfuric acid and boil the solution meets the U S P test for arsenic. Dissolve 10 Gm of aluminum phosphate gel in 10 cc of diluted sulfuric acid the resultant solution conforms to the U S P test for heavy metals.

Transfer 25 cc of aluminum phosphate gel to a beaker add 5 cc of nitric acid 50 cc of distilled water and 40 cc of tenth normal silver nitrate.  
 and titrate  
 titration  
 does  
 of fifth  
 nitric acid and 20 cc of ammonium molybdate solution. Digest on the steam bath for one hour filter and wash the precipitate with 2 per cent nitric acid followed by washing with 1 per cent potassium nitrate solution until the filtrate is no longer acid. Dissolve the

wash the precipitate  
 with cyanate solution  
 the chloride content  
 gel to yield 100 cc  
 beaker add 2 cc of

to p 25. Each gram of the gel requires no less than 5 nor more than 9 cc of tenth normal hydrochloric acid. Transfer about 20 Gm of aluminum phosphate gel accurately weighed to a 100 cc volumetric flask add nitric acid until solution is complete and dilute to the mark. Meticulously transfer 10 cc to a 400 cc beaker dilute to 100 cc warm to 80 C add an excess of ammonium molybdate solution and digest on the steam bath for one hour filter and wash the precipitate with 2 per cent nitric acid followed by 1 per cent potassium nitrate solution until the filtrate is no longer acid. Dissolve the precipitate in one half normal sodium hydroxide and titrate with one half normal acid using phenolphthalein as the indicator. Each cubic centimeter of one half normal sodium hydroxide is equivalent to 2.654 mg of AlPO. The calculated aluminum phosphate content is no less than 3.8 nor more than 4.2 per cent.



JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED

**Phosphaljel:** 480 cc. bottle. Aluminum phosphate gel containing 4 per cent of aluminum phosphate, 5 per cent of glycerin, not more than 0.5 per cent of sodium benzoate as a preservative and oil of peppermint as a flavoring agent.

**TRIBASIC CALCIUM PHOSPHATE-U. S. P.**—Precipitated calcium phosphate.—“After ignition to a constant weight, contains an amount of phosphate ( $\text{PO}_4$ ) corresponding to not less than 90 per cent of  $\text{Ca}_3(\text{PO}_4)_2$ .” U. S. P.

For description and standards see the U. S. Pharmacopeia under *Calcii Phosphas Tribasicus*.

**Actions and Uses**—Tribasic calcium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate, in that, being less soluble it tends to neutralize the excess of acid in the stomach but produces less systemic alkalinization. It has been claimed that tribasic calcium phosphate is somewhat constipating. It has been shown that some of the calcium is absorbed, hence this salt may be used to obtain the therapeutic effects of calcium

**Dosage**—From 1 to 5 Gm

MERCK & Co., Inc.

**Calcium Phosphate Tribasic (Powder):** bulk

**MAGNESIUM TRISILICATE.**—“Contains not less than 20 per cent of magnesium oxide ( $\text{MgO}$ ) and not less than 45 per cent of silicon dioxide ( $\text{SiO}_2$ ).” U. S. P.

For description and standards see the U. S. Pharmacopeia under *Magnesium Trisilicas* and *Tabellae Magnesii Trisilicatis*

**Actions and Uses.**—It neutralizes the hydrochloric acid of the gastric juice by chemical action. It possesses adsorptive properties, but it does not interfere with peptic digestion nor does it usually induce alkalosis. It is nontoxic in ordinary amounts, but large doses sometimes induce diarrhea because of the magnesium chloride formed. It is used for the relief of gastric hyperacidity and pain in gastric and duodenal ulcer.

**Dosage**—From 1 to 4 Gm. before meals or food taken at other times, the single dose and the frequency of repetition depending on the degree of acidity and the relief afforded

BURROUGHS WELLCOME & Co., Inc.

**Tablets Magnesium Trisilicate:** 0.486 Gm.

THE LAKESIDE LABORATORIES, INC.

**Tablets Magnesium Trisilicate:** 0.49 Gm.

## MALLINCKRODT CHEMICAL WORKS

Magnesium Trisilicate (*Powder*)· bulk

## THE SMITH DORSEY COMPANY

Tablets Magnesium Trisilicate 0.324 Gm

## TRIBASIC MAGNESIUM PHOSPHATE-U S P—

‘When ignited to constant weight contains not less than 98 per cent of  $Mg_3(PO_4)_2$ ’ U S P

For description and standards see the U S Pharmacopeia under Magnesium Phosphas Tribasicus

*Actions and Uses*—Tribasic magnesium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate in that being soluble it neutralizes the excess of acid in the stomach but does not produce systemic alkalization. It has been claimed that tribasic magnesium phosphate has a laxative action.

*Dosage*—From 1 to 5 Gm

## MERCK &amp; Co, INC

Magnesium Phosphate Tribasic (*Powder*) bulk

## Emollients

**GASTRIC MUCIN**—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin hydrochloric acid digestion of hog stomach linings.

*Actions and Uses*—Gastric mucin is prepared for use in the treatment of peptic ulcers.

*Dosage*—Average dose 2.5 Gm which can be given at two hour intervals.

*Tests and Standards*—

Gastric mucin occurs as a white to yellow powder or brownish yellow granules. It possesses a slightly salty taste and characteristic odor indicative of peptones. Both forms yield a viscous gray opalescent solution when triturated with water.

Dry approximately 1 Gm of gastric mucin accurately weighed to constant weight at 100 C the loss in weight does not exceed 6 per cent.

Incinerate approximately 1 Gm of gastric mucin accurately weighed in a muffle furnace at 500 C the ash content does not exceed 6.5 per cent.

Determine the nitrogen content in the dried alcohol insoluble residue (described in the foregoing paragraph) by the Kjeldahl method according to Methods of Analysis of the Association of Official Agricultural Chemists, ed. 4, page 23: the nitrogen content is not less than 7.0 nor more than 9.0 per cent.

Transfer 0.1 Gm. of the dried alcohol insoluble residue as previously obtained to a 125 cc. Erlenmeyer flask and add 50 cc. of two-normal sulfuric acid. Digest on a steam bath under a reflux condenser for three hours and dilute to 100 cc. Transfer 4 cc. of this solution to a 25 by 200 mm. test tube, add 1 drop of phenolphthalein and neutralize with 30 per cent sodium hydroxide. Add 5 cc. of standard copper reagent [Twenty-five Gm. of anhydrous sodium carbonate, 20 Gm. of sodium bicarbonate and 25 Gm. of sodium potassium tartrate is dissolved in 600 cc. of distilled water; 7.5 Gm. of  $\text{CuSO}_4 \cdot \text{H}_2\text{O}$  is dissolved in 100 cc. of water and introduced with constant stirring into the carbonate-tartrate solution through a funnel resting on the bottom of the con-

determination should not be less than 8.6 nor more than 12.2 cc.; that is, not less than 25 per cent nor more than 35 per cent of reducing material, calculated as dextrose in the alcohol insoluble material.

Prepare a 2 per cent solution of gastric mucin by triturating 2 Gm. of mucin with 100 cc. of water and passing it through a 60 mesh screen. Determine the pH of this solution by means of a glass electrode at 25 C.; the pH is not below 3.7 nor above 6.5. Determine the viscosity of this solution at 25 C. within one hour by means of a 10 cc. Mohr pipet and compare it with water: the relative viscosity is not below 1.30 nor above 3.50.

Gastric mucin is manufactured by license from the Gastric Mucin Committee of Northwestern University Medical School under U. S. patent 1,829,270 (Oct. 27, 1931; expires 1948).

#### THE ARMOUR LABORATORIES

Gastric Mucin (*Powder or Granules*): bulk.

#### FREDERICK STEARNS & COMPANY

Gastric Mucin (*Powder or Granules*): bulk.

#### THE WILSON LABORATORIES

Gastric Mucin (*Powder or Granules*): bulk.

**MAGMA OF BISMUTH.**—"Magma of Bismuth contains bismuth hydroxide and bismuth subcarbonate in suspension in water and yields not less than 5.2 per cent and not more than 5.8 per cent of  $\text{Bi}_2\text{O}_3$ ."—*N. F.*

For description and standards see The National Formulary under Magma Bismuth.

*Dosage*—From 4 to 15 cc. every two or three hours.

E. J. HART & Co., Ltd

Lac Bismo Magma of Bismuth  
U. S. trademark 52 250

SHARP & DOHME, INC

Crema-Bismuth Magma of Bismuth  
U. S. trademark 29 335

### Laxatives

**AGAR** — Agar Agar — The dried mucilaginous substance extracted from *Gelidium corneum* (Hudson) Lamouroux and other species of *Gelidium* (fam. *Gelidiaceae*) and closely related algae (Class *Rhodophyceae*). Agar contains not more than 1 per cent of foreign organic matter, and yields not more than 1 per cent of acid insoluble ash and not more than 20 per cent of moisture when determined by the toluene method IX  
U. S. P.

For description and standards see the U. S. Pharmacopeia under Agar

MENCH & Co., Inc

Agar-Agar (*Powder and Shreds*) bulk

**LIQUID PETROLATUM** — Liquid Paraffin — White Mineral Oil — Heavy Liquid Petrolatum — A mixture of liquid hydrocarbons obtained from petroleum U. S. P.

For description and standards see the U. S. Pharmacopeia under Petrolatum Liquidum and Emulsum Petrolati Liquidum and the National Formulary under Emulsum Petrolati Liquidum Phenolphthaleino

*Actions Uses and Dosage* — See Useful Drugs

PETROGALAR LABORATORIES, INC

**Petrogalar** Liquid petrolatum (5 cc emulsified with 0.4 Gm agar agar in a menstruum containing glycerin acacia saccharin flavoring benzoic acid and water to make 100 cc. Contains sodium benzoate 0.06 per cent as preservative

**Alkaline Petrogalar** Petrogalar with magnesium magma 8 cc per 100 cc. No saccharin or preservative

**Cascara Petrogalar** Petrogalar with non-litter fluid extract of cascara sagrada 13.2 cc per 100 cc and sodium benzoate 0.07 per cent as preservative

**Phenolphthalein Petrogalar** Petrogalar with phenolphthalein 0.32 Gm. Contains 0.05 per cent as preservative

**Unsweetened Petrogalar** Petrogalar with saccharin omitted. Contains sodium benzoate 0.06 per cent as preservative

U. S. trademark 165 616

**THE SMITH-DORSEY COMPANY**

**Emulsion Liquid Petrolatum, Chocolate Flavored:** A palatable emulsion containing 60 per cent (by volume) of liquid petrolatum, 1 per cent agar-agar per 30 cc. and 0.1 per cent of benzoic acid.

**Emulsion Liquid Petrolatum with 0.1 Gm. Phenolphthalein, Chocolate Flavored.**

**Emulsion Liquid Petrolatum with 0.3 Gm. Phenolphthalein, Chocolate Flavored.**

**SMITH OIL & REFINING CO.**

**Mineral Oil:** bulk.

**E. R. SQUIBB & SONS**

**Mineral Oil:** 180 cc., 480 cc. and 960 cc. bottles.

**Mineral Oil Emulsion:** Mineral oil, 50 cc.; agar, 0.75 Gm; karaya, 0.75 Gm; sodium benzoate, 0.1 Gm; acacia, glycerin, water and flavoring sufficient to make 100 cc.

**Mineral Oil Emulsion and Phenolphthalein:** Mineral oil emulsion with 0.31 Gm phenolphthalein per 100 cc.

U. S. patent 1,799,804 (April 7, 1931; expires 1948) and 1,913,561 (June 13, 1933, expires 1950).

**PETROLATUM.**—Petroleum Jelly.—“A purified, semi-solid mixture of hydrocarbons obtained from petroleum”  
U. S. P.

For description and standards see the U. S. Pharmacopœia under Petrolatum

**SARGENT'S DRUG STORE**

**Petrobran:** Each 100 Gm contains: petrolatum, 74 Gm.; bran, 22 Gm.; with powdered licorice and “oil of pineapple” (ethyl butyrate) sufficient to flavor.

**PLANTAGO SEED.**—*Psyllium Seed.*—Plantain Seed.—“The cleaned, dried, ripe seed of *Plantago Psyllium* Linné, or of *Plantago arenaria* Waldstein et Kitaibel (*P. ramosa* [Gilib] Aschers), known in commerce as Spanish or French *Psyllium Seed*; or of *Plantago ovata* Forskal, known in commerce as *Blonde Psyllium* or *Indian Plantago Seed* (Fam. *Plantaginaceæ*)”  
“*Plantago Seed* contains all of its natural mucilage and not more than 0.5 per cent of foreign organic matter. It yields not more than 4 per cent of total ash and not more than 1 per cent of acid-insoluble ash.” *N. F.*

For description and standards see the National Formulary under *Plantaginis Semen*

**Actions and Uses.**—*Plantago seed*, by virtue of its indigestibility and mucilaginous character, acts as a mild laxative. The addition of ground plantago seed to the food of rats and dogs

has been found to be followed by darkening of the kidneys and when prolonged its use was followed by the appearance of microscopic pigment granules in the tubules of rats. The significance of this has not been determined.

*Dosage*—From 4 to 15 Gm. one to three times a day. Plantago seed may be mixed with orange juice or prune juice and eaten without mastication or the dose may be mixed with a little hot water and the resulting gelatinous mass spread on bread or taken with other food.

RICHARDS PHARMACAL Co., Inc.

*Psyllium Seed* bulk

SCHIEFFELIN & Co.

*Psyllium Seed* bulk

## CHAPTER XV

### HEMATICS

#### Iron and Iron Compounds

Iron is used in medicine: (1) in the form of metallic or elementary iron (reduced iron, U. S. P.); (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate and pill of ferrous carbonate, ferrous iodide in syrup of ferrous iodide); (3) in the trivalent or oxidized form, the ferric compounds—responding to tests for ferric ions (ferric chloride in tincture of ferric chloride); and (4) in the form of complex compounds of iron.

Complex (masked or nonionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the astringent taste of simple iron solutions. The permanence of these complex radicals differs widely; while some, such as soluble ferric phosphate, N. F., and solution of peptonized iron, N. F., are converted to simple ionic iron by action of dilute acids, others resist treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp line of distinction between the natural complex iron compounds and the artificially produced ones, nor is there any good evidence that they differ in therapeutic action. Until a difference in their effects has been demonstrated, we may class together all complex iron compounds whose solutions are not decomposed into simple ionic iron by digestion at body temperature with 0.2 per cent hydrochloric acid and pepsin. (It should be emphasized that salts of iron which give the iron test directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds.)

*Actions and Uses*—Solutions of ferric iron are used externally as styptics. Tincture of ferric chloride is an astringent and is used in applications to the throat. The principal use of iron, however, is in the treatment of anemia and chlorosis. For this purpose, the ferrous salts are usually preferred to the ferric salts, as they are not so caustic and hence are less likely to disturb the stomach. Reduced iron, yielding ferrous chloride when dissolved in the stomach, acts as a ferrous compound, provided the hydrochloric acid in the gastric fluid is sufficient to permit solution. So far as the complex iron compounds are not decomposed by gastric digestion, they also are devoid of

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per cent aqueous solution of the salt should not yield more than a faint opalescence with a lead acetate solution (*limit or absence of sulfate, chloride, citrate, tartrate and malate*). The aqueous solution after acidulation with hydrochloric acid should not yield any precipitate or coloration when treated with hydrogen sulfide (*foreign metals*). The aqueous solution, acidulated with nitric acid, should not afford more than slight opalescence with barium chloride solution or with silver nitrate solution (*limit of sulfate or chloride*). If 25 cc. of a 2 per cent aqueous solution of the salt is mixed with 5 cc. of diluted sulfuric acid, the mixture boiled for a few minutes, an excess of sodium hydroxide solution added and the mixture filtered, the filtrate, when mixed with a few drops of alkaline cupric tartrate solution and boiled, does not yield a red precipitate (*sugar*). If a portion of the salt is triturated with sulfuric acid, no offensive odor is developed (*butyric acid*), nor is any gas evolved (*carbonate*) and the mixture, after standing for some time, does not assume a brown color (*sugar, gum or other readily carbonizable impurities*). If from 1 to 1.5 Gm. of the salt is weighed and moistened with nitric acid and carefully ignited in a porcelain crucible it leaves a residue of ferric oxide, weighing not less than 27 per cent nor more than 27.8 per cent of the material taken; this residue does not have an alkaline reaction on litmus paper, nor yield anything soluble to water (*foreign salts*).

MENCK & Co., INC.

Iron Lactate (*Crystals*): bulk.

### Complex Iron Salts

**IRON AND AMMONIUM CITRATES.**—“Contains ferric citrate equivalent to not less than 16.5 per cent and not more than 18.5 per cent of Fe”—U. S. P.

For description and standards see the U. S. Pharmacopeia under *Ferri et Ammonii Citrates* and *Capsulae Ferri et Ammonii Citratum*.

*Actions and Uses.*—See preceding article, Iron and Iron Compounds. Iron and ammonium citrates is a hematinic which is practically nonastringent.

*Dosage*—1 Gm

THE UPJOHN COMPANY

Capsules Iron and Ammonium Citrates: 0.5 Gm. (7½ grains).

### Pentnucleotide

**PENTNUCLEOTIDE.**—The sodium salts of the pentose nucleotides from the ribonucleic acid of yeast. Pentnucleotide is prepared from yeast nucleic acid by hydrolysis for twenty-four hours with 1 per cent sodium hydroxide solution. The lead salts prepared from the acidified hydrolyzed solution are decomposed with hydrogen sulfide and the liberated acids are concentrated and precipitated with alcohol. The sodium salts are prepared by neutralization with sodium hydroxide. The final product is approximately an 8 per cent solution of the sodium salts of what appear to be four nucleotides; the solution has a  $pH$  of 7.2 and is preserved with tricresol, 0.3 per cent.

*Actions and Uses.*—Pentnucleotide is indicated in infectious conditions accompanied by leukopenia or neutropenia, such as

agranulocytosis (agranulocytic angina, idiopathic pernicious leukopenia)

It is now recognized that the vast majority follow the use of chemotherapeutic agents such as pyrimine, acetylsalicylic acid, nitrophenol and are repeatedly incriminated. More recently it is extreme leukopenia occasionally developing agranulocytosis, is one of the most common reactions caused by sulfonamide therapy.

With a total white count below 2,500, be used moderately when the differential is significant reduction in polymorphonuclear leukemic leukemia and aplastic anemia.

**Dosage**—The contents of one vial should be injected undiluted into the gluteal muscle daily. The recommended four vials are continued until the temperature has appeared not only in the total white count but also in the percentage of polymorphonuclear leukocytes. In many cases this usually occurs in from 3 to 5 days after the initiation of treatment. In some young polymorphonuclears may appear after beginning pentamucleotide, but the blood picture in four or five days is a indication that a favorable clinical result. If there has been no response at 10 days of therapy with pentamucleotide is pred

After a favorable response to (daily) has been obtained one will treat once or twice daily until the been normal for several days. It resumed if the white blood cell,

Although reactions such as bradycardia, sweating or vomiting or febrile reaction immediate as they occur infrequently and are ecotide is given intramuscular occur, they may be minimized small divided doses into an an

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#### Tests and Standards—

Pentnucleotide is a clear pale yellow. The dry salt is very hygroscopic.

Treat 10 cc of pentanucleot de  
boil the mixture for two minutes  
the vapors acquires a rose red  
the solution with stronger ammonia  
chloric acid filter, make alkaline  
a precipitate forms on standing  
water moisten with 10%  
porcelain dish on  
solution (10 per  
rose or

ature 1794-1800  
annual, prepared  
in practice by  
the below.  
Edm. Clements

of any  $\mathbb{P}^1$  can be

ammoniacal filtrate add 5 cc. of 10 per cent calcium chloride solution and wash with water; add 1 cc. of wash with 2 cc. of water; to the ammonium molybdate solution a precipitate forms on gentle warming (phosphates).

coloration is produced (biuret); add 1 cc. of 1 per cent copper sulphate solution; no marked precipitate is produced (gums). To 5 cc. of pentnucleotide add 1 cc. of diluted hydrochloric acid and an equal volume of freshly prepared hydrogen sulphide water; treat according to U. S. P. test for heavy metals: no more color change is shown than when 5 cc. of pentnucleotide is treated with 1 cc. of diluted hydrochloric acid and an equal volume of water. To 5 cc. of pentnucleotide add several drops of silver nitrate solution (10 per cent): a white precipitate forms, which dissolves on shaking the mixture.

To 5 cc. of pentnucleotide add 10 cc. of lead acetate solution and 0.2 cc. of glacial acetic acid, a white precipitate forms. Agitate the mixture for one or two minutes and filter with suction; wash the precipitate well with water, suspend in 15 cc. of distilled water, and treat with excess hydrogen sulphide; stir well, and filter into a tared flat shallow weighing dish, evaporate nearly to dryness on the steam bath; add about 5 cc. of dehydrated alcohol, evaporate the alcohol, then dry in a vacuum desiccator over sulphuric acid to constant weight; dissolve the dried substance in 10 cc. of water; add one drop of phenolphthalein indicator solution and titrate with tenth normal sodium hydroxide solution not more than 63.5 cc. nor less than 57.5 cc. of tenth normal sodium hydroxide is consumed per gram of dried substance. Evaporate a 5 cc. portion of pentnucleotide to constant weight in a tared shallow dish over a steam bath; not more than 0.45 Gm, nor less than 0.41 Gm of solid residue results.

## SMITH, KLINE & FRENCH LABORATORIES

Vials Pentnucleotide: 10 cc

U S trademark 301,527

## Fibrin Ferments and Thromboplastic Substances

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood. The fibrin ferment of thrombin exists in the blood in the form of its forerunner (prothrombin) which is acted on by the calcium salts and converted into thrombin. Besides calcium salts, however, another factor is necessary. This other factor may be furnished by the breaking down of blood cells or blood platelets or by injured tissues. It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinas" by Morowitz, and as "thromboplastic substance" or "thromboplastin" by Howell.

It is generally agreed that in the conversion of inactive prothrombin to active thrombin both thromboplastic substance and calcium ions are concerned, but the precise nature of the reaction is undetermined. It is variously interpreted in the different theories of coagulation that have been proposed.

The chemical nature of thromboplastic substance is also a matter of controversy. This material is readily extracted from fresh or dried tissues by aqueous solutions, and from dried or dehydrated tissues by the action of alcohol, ether or other lipid solvents. The aqueous extracts contain protein and are much more potent than those obtained with lipid solvents. It is characteristic of both kinds of extracts that their thromboplastic action undergoes a gradual deterioration when kept exposed to air. In the extracts made with alcohol, ether, etc., the active component was formerly believed to be lecithin, but Howell, Gratia and Levene and others have shown that purified lecithin is devoid of thromboplastic activity. On the other hand cephalin as usually prepared has marked thromboplastic properties, and the general view has been that this thromboplastic substance present in the tissues and blood platelets is a water soluble protein cephalin compound or complex. Such a compound has, however, not been isolated in a condition of chemical purity, and the real nature of thromboplastin is still a subject for investigation, although it seems probable that it is a combination, of some kind, between a protein and a phospholipid.

*Actions and Uses*—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhage, especially hemorrhage from oozing surfaces, like wise in the treatment of scar tissues in nosebleed, and in surgery of the bones, glands nose and throat, but many surgeons have abandoned their use even for such purposes. Intravenous injection is probably dangerous, and there is no satisfactory evidence that subcutaneous injection is useful. Preparations should be standardized by testing specimens of blood *in vitro* and should reduce the coagulation time significantly. They should be proved to be sterile. The Council holds that there is no evidence to warrant the internal use of these substances, and further that such use on account of the danger from anaphylaxis from preparations containing animal proteins, is likely to be harmful unless proper precautions are taken. There appears to be no evidence that this danger is connected with local applications, but even before such use physicians should inquire into the patient's history to determine whether or not sensitivity to these proteins exists.

**BRAIN LIPOID**—Impure Cephalin—Impure Nephalin—An extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelder (*Lancet* 2 542, 1915) and described below.

*Actions and Uses*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage*—Brain lipid may be spread on gauze sponges on pledgets or on the tissues themselves or an emulsion may be prepared by shaking up with physiological solution of sodium chloride and used in the same way or sponged over the tissues.

For use in an office or dispensary, a 5 per cent ethereal solution of brain lipid suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from which an opalescent emulsion can be prepared extemporaneously by dropping from 10 to 30 drops into an ounce of physiological solution of sodium chloride and then shaking. This solution can also be dispensed by pharmacists, provided the opening in the stopper of the dropper bottle is kept slightly open to prevent the ether's blowing off when the bottle is shaken or heated.

#### *Tests and Standards.—*

Brain lipid (impure cephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol and agitated two or three times. The excess of alcohol is then poured off and squeezed out gently through linen, care being taken to avoid great force in wringing out the alcohol, as this tends to break up the brain tissue into very finely divided particles which pass through the filter. The residue is then covered with 3 volumes of ether, shaken vigorously and filtered first through cotton and then through filter paper. The clear filtrate thus obtained is evaporated to dryness over a water bath, leaving a yellow residue of fatty appearance and consistency. (This residue consists largely of cephalin, but though the latter is not in the pure state, it is extremely active in accelerating the clotting of blood *in vitro*.)

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activities for several weeks.

(The impurities, largely the lecithins and myelins, do not materially interfere with the activity of the cephalin, but, on the contrary, facilitate its emulsification in physiological solution of sodium chloride and thus facilitate its intimate miscibility with blood.)

**FIBROGEN LOCAL.**—Suspension of Tissue Fibrinogen and Cephalin for Local Use.—A sterile suspension of tissue fibrinogen and cephalin, containing 1.5 per cent tissue fibrinogen and 0.5 per cent cephalin in a solution of sodium chloride 0.9 per cent.

*Actions and Uses.*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—Fibrogen Local is applied locally, undiluted.

#### *Preparation.—*

Fresh beef lungs are finely ground and extracted in the cold with 10 per cent sodium chloride solution. To the filtered extract is added an equal volume of saturated ammonium sulfate solution. The globulin fraction containing the tissue fibrinogen is precipitated and removed by filtration. Fibrogen is prepared from a 15 per cent dry weight suspension of this material in physiological saline. Complete sterilization is accomplished by the addition of bichloride of mercury the greater part of which is subsequently removed by dialysis. After most of the mercury has been removed so that less than 1 part in 3,500 remains, sodium chloride is added to make a final concentration of the latter 0.9 per cent. The amount of the residual mercury is determined by a modification of the method which is described in the Official & Tentative Methods of Analysis.

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The potency of fibrinogen Local is determined by measuring its power to accelerate the clotting of recalcified citrated or oxalated plasma or of blood. By the above tests the coagulation time is found to be reduced approximately 90 per cent.

The following is a description of the method employed for measuring the thromboplastic activity of Fibrinogen Local

10 cc of blood are drawn from the heart of a rabbit into an oiled syringe. The blood is then transferred in 10 cc quantities into each of 10 test tubes which are maintained at 37°C. To each tube is added 1 cc of 1% saline and to each tube 1 cc of 1% Fibrogen Local. The blood which has been added will coagulate in approximately 15 to 25 minutes to clots. The time of coagulation of the blood, therefore, has been reduced approximately 90 per cent through the action of 1 cc of Fibrogen Local.

THE WM. S. MERRILL COMPANY

Fibrogen Local, 7 cc vials

U S patent number 16 619    U S trademark 208 121

**SOLUTION BRAIN EXTRACT**—Liquor Extracti Cerebri—Solution Thromboplastin Hess—An extract of cattle brain in physiological solution of sodium chloride prepared by the method of Hess (*J A M A* 66 558 [Feb 19] 1916 foot note 2)

**Actions and Uses**—See preceding article, Fibrin Ferments and Thrombolytic Substances

**Dosage**—The solution may be applied directly to the bleeding tissues or sprayed on them or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

**Preparation —**

Cattle brains are obtained fresh from the slaughter house, stripped of their membranes, washed in running water and weighed. They are

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## LEDERLE LABORATORIES, INC.

Thromboplastin Local 20 cc vials

*Tests—*

The potency of thromboplastin local Lederle is tested as follows: Transfer 0.5 cc of oxalated blood plasma (0.1 per cent oxalate) to each of a series of tubes and add 0.2 cc of thromboplastin local Lederle to each tube. Also transfer 0.5 cc of oxalated blood plasma to each of a control series of tubes and add 0.2 cc of physiologic solution of sodium chloride. To each tube (and control) add 0.2 cc of calcium chloride solution the strength of which is determined by

*Powders for Oral Administration*

**EXTRACT OF LIVER.**—Dry Liver Extract.—"Contains that soluble thermostable fraction of mammalian livers which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The approximate anti-anemic potency of Extract of Liver in pernicious anemia shall be expressed in U. S. P. Units and shall conform to all other provisions outlined under Anti-anemia Preparations." U. S. P.

*Actions and Uses.*—Extract of liver is used in the treatment of pernicious anemia. See general article, Liver and Stomach Preparations.

*Dosage.*—Extract of liver is administered orally. The average daily maintenance dose should not be less than the amount required to provide 1 U. S. P. oral unit. In relapse and in severe or complicated cases larger doses may be necessary. In cases where several units daily are indicated to induce prompt remission, the required dosage may be more feasibly supplied by the administration of injectable preparations. Oral administration is therefore more suited for maintenance requirements when the inconvenience of repeated intramuscular injection to the patient does not outweigh the objection to the taste of the dried extract. The taste may be masked by suspending each dose of the powder in half a glass of milk or fruit juice.

**ARMOUR LABORATORIES**

**Capsules Liver Extract Concentrate:** 0.5 Gm. in 0.37 Gm of corn oil. A suspension of extract of liver U. S. P. in corn oil marketed in capsules. Each capsule (0.5 Gm. of extract of liver) represents a potency of  $\frac{1}{16}$  U. S. P. oral unit.

**ELI LILLY AND COMPANY**

**Liver Extract (Powder):** 4.2 Gm vial and 110 Gm bottle. Each 1275 Gm (3 vials) represents 1 U. S. P. oral unit.

**PANKE, DAVIS & COMPANY**

**Liver Extract (Powder):** 3 to 3.5 Gm. vial. Each 18 to 21 Gm (six vials) represents 1 U. S. P. oral unit.

**EXTRALIN.**—A liver-stomach concentrate resulting from the interaction of a mammalian concentrated liver extract containing the Cohn fraction D and stomach tissue material. The daily oral administration of 6 Gm has been found to produce the standard reticulocyte response defined as 1 U. S. P. unit (oral) when assayed in cases of pernicious anemia as required by the Council.

*Actions and Uses.*—Extralín is proposed for use in the oral treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

**Dosage**—For cases of pernicious anemia in relapse an initial dosage of 2 Gm (four pulvules) three times daily is suggested, 15 Gm (three pulvules) three times daily constitutes an adequate maintenance dose for most cases. The amount necessary for maintenance varies with different individuals and can be determined only after repeated examinations.

**Preparation**—

An extract containing the Cohn fraction D is prepared by grinding mammalian livers into water adjusting the mixture to the iso electric point (approximately pH 5 to pH 6) and heating to about 80 C to coagulate protein. This is stirred for thirty minutes and filtered. The filtrate is reduced under vacuum to small volume. This extract is then admixed with finely minced fresh hog stomachs or fresh hog stomach linings. The hydrogen ion concentration is adjusted to approximately pH 5 and the mixture allowed to interact or digest for about two hours at 37.5 C. It is then spread out in a thin layer on pans and dried under vacuum. The dried product is removed from the drier and ground then extracted with petroleum ether to remove fat. This is dried under vacuum and ground to the proper fineness. The proportions used are such that there is represented in the finished product two to four parts of original liver to one part of original stomach tissue material.

**FLI LILLY AND COMPANY**

**Pulvules Extralin** 0.5 Gm. Twelve pulvules supply the equivalent of 1 U S P oral unit of liver.

U S patent 1,894,247 (Jan. 10, 1933 expires 1950) U S trade mark 290,233

**POWDERED STOMACH**—Dried Stomach—The dried and powdered defatted wall of the stomach of the hog *Sus scrofa* Linne var *Domesticus* Gray (Fam. Suidae). It contains factors which cause an increase in the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The approximate anti anemic potency of Powdered Stomach in pernicious anemia is expressed in U S P Units and conforms to all other provisions outlined under Anti anemia Preparations. U S P

**Actions and Uses**—Dried stomach is used in the treatment of pernicious anemia. See preceding article Liver and Stomach Preparations.

**Dosage**—The average daily dose should not be less than the amount required to furnish 1 U S P oral unit. Larger doses may be necessary in relapse and in severe or complicated cases. The required doses may be administered in a half glassful of water, milk or fruit juice.

**PARKE DAVIS & COMPANY**

**Ventriculin** 10 Gm vial 100 Gm and 500 Gm bottles. Dried stomach 40 grams of material prepared by the method employed in producing the contents of this bottle constitutes 1 U S P unit (oral).

U S patent 1,937,133 U S trademark 270,811



*Solutions for Oral Administration*

**SOLUTION OF LIVER.**—Liquid Extract of Liver.—“Contains that soluble thermostable fraction of mammalian livers which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The approximate anti-anemic potency of Solution of Liver in pernicious anemia is expressed in U. S. P. Units and conforms to all other provisions outlined under Anti-anemia Preparations.” U. S. P.

*Actions and Uses*—Solution of liver is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations

*Dosage.*—Solution of liver is administered orally. The average daily dose should not be less than the quantity required to supply 1 U. S. P. oral unit. Patients in relapse or with complications often need larger doses which may be more conveniently furnished by supplementing or substituting the oral treatment with the administration of injectable preparations until the blood picture is restored to normal. Like the dry preparations for oral use, solution of liver is better suited for maintenance therapy and when there is some objection to repeated injections. The solution may be administered with milk or fruit juice.

**THE ARMOUR LABORATORIES**

**Solution Liver Extract:** 236.5 cc. and 473 cc. bottles  
A solution of the water-soluble fraction extracted from fresh mammalian liver. Each 45 cc. represents 1 U. S. P. oral unit

**LEDBETTER LABORATORIES, INC.**

**Solution Liver Extract Oral:** A hydro-alcoholic solution of the active principle extracted from mammalian liver. Each 60 cc represents 1 U. S. P. oral unit

**THE UPJOHN COMPANY**

**Liver Liquid Extract Oral:** 236.5 cc. bottle A solution of the water soluble fraction extracted from mammalian liver. Each 45 cc represents 1 U. S. P. oral unit

**VALENTINE COMPANY, INC.**

**Liquid Extract of Liver:** A solution of the water-soluble fraction extracted from mammalian liver. Each 45 cc represents 1 U. S. P. oral unit

U. S. trademark 298,963

*Solutions for Parenteral Administration*

**LIVER INJECTION.**—Liver Extract for Parenteral Use.—“A sterile solution in water for injection of that soluble thermostable fraction of mammalian livers which increases the

number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The approximate anti-anemic potency of Liver Injection upon parenteral administration in pernicious anemia is expressed in U S P Units and conforms to all other provisions given under Anti-anemia Preparations U S P.

*Actions and Uses*—Liver Injection is used for intramuscular injection in the treatment of pernicious anemia. See preceding article Liver and Stomach Preparations.

*Dosage*—For the average case in relapse it is usually advisable to administer an initial injection of the amount which will provide 20 to 40 U S P injectable units. This may be divided into daily injections of 10 to 20 units each for two or four successive days depending on the severity of the individual case. In seven to ten days after the initial treatment weekly injections of the amount necessary to furnish 10 U S P injectable units are generally sufficient to induce complete remission. The maintenance dose should not be less than the quantity required to provide 1 U S P injectable unit daily or an equivalent cumulative amount. In complicated cases and those with extensive neurologic involvement the optimum dose may be larger and must be determined for each patient. In patients which are to receive larger doses it may be advisable to divide the required amount and inject one half into each gluteal region.

#### ABBOTT LABORATORIES

**Liver Extract (Injectable) 5 U S P Units per Cc**  
10 cc and 50 cc vials. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**Liver Extract (Injectable), 10 U S P Units per Cc**  
5 cc, 10 cc and 30 cc vials. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

#### THE ARMOUR LABORATORIES

**Liver Liquid Parenteral 4 U S P Units per Cc**  
1 cc, 5 cc and 10 cc vials. A sterile aqueous purified solution of liver preserved with 0.3 per cent cresol.

**Liver Liquid Parenteral 15 U S P Units per Cc**  
1 cc, 5 cc and 10 cc rubber capped vials. A sterile aqueous solution of liver preserved with 0.5 per cent phenol.

#### GEORGE A. BREON & COMPANY, INC.

**Purified Solution of Liver, 10 U S P Units per cc**  
5 cc and 30 cc vials. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**Purified Solution of Liver, 5 U S P Units per cc**  
10 cc vial. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**BUFFINGTON'S, INC.**

**Purified Solution Liver, 10 U. S. P. (Injectable) Units per Cc.:** 10 cc. vial. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**THE DRUG PRODUCTS CO., INC.**

**Hyposols Solution Liver Purified, 10 U. S. P. Units per Cc.:** 1 cc. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**Solution Liver Purified, 10 U. S. P. Units per Cc.:** 10 cc. vials. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**ENDO PRODUCTS, INC.**

**Liver Extract (Injectable), 2 U. S. P. Units per Cc.:** 10 cc. vials. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**Ampoule Liver Extract (Injectable), 5 U. S. P. Units per Cc.:** 1 cc. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**Ampoule Liver Extract (Injectable), 10 U. S. P. Units per Cc.:** 1 cc. A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol.

**Liver Extract (Injectable), 10 U. S. P. Units per Cc.:** 10 cc. vial. A sterile aqueous purified solution of liver, preserved with 0.5 per cent phenol.

**FLINT, EATON & COMPANY**

**Liver Injection (Crude) 1 and 2 U. S. P. Units per Cc.:** 15 cc. and 30 cc. multiple dose vial. A sterile aqueous, purified solution of liver preserved with 0.5 per cent phenol.

**THE LAKESIDE LABORATORIES, INC.**

**Ampule Purified Solution of Liver, 10 U. S. P. Injectable Units per cc.:** 1 cc. A sterile aqueous solution of liver preserved with 0.5 per cent of phenol.

**Purified Solution of Liver, 10 U. S. P. Injectable Units per cc.:** 10 cc. vial. A sterile aqueous solution of liver preserved with 0.5 per cent of phenol.

**Purified Solution of Liver, 2 U. S. P. Injectable Units per cc.:** 60 cc. vial. A sterile aqueous solution of liver preserved with 0.5 per cent of phenol.

**LEDERLE LABORATORIES, INC.**

**Solution Liver Extract Parenteral, 3.3 U. S. P. Units per Cc.:** 3 cc. vial. A sterile aqueous purified solution of fresh mammalian liver preserved with 0.5 per cent phenol.

**Refined Solution Liver Extract Parenteral, 10 U S P Units per Cc** 5 cc and 10 cc vials A sterile aqueous purified solution of fresh mammalian liver preserved with 0.5 per cent phenol

**Concentrated Solution Liver Extract Parenteral, 15 U S P Units per Cc** 1 cc 3 cc and 10 cc vials A sterile aqueous purified solution of fresh mammalian liver preserved with 0.5 per cent phenol

#### ELLI LILLY AND COMPANY

**Solution Liver Extract Crude, 1 U S P Unit per Cc** 10 cc rubber stoppered ampuls A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol prepared by dilution of the 2 U S P unit product with an equal quantity of water

**Solution Liver Extract Crude 2 U S P Units per Cc** 3.5 cc and 10 cc rubber stoppered ampuls A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol

**Solution Liver Extract Purified 5 U S P Units per Cc** 10 cc rubber stoppered ampuls A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol prepared by dilution of the 15 U S P unit product with water

**Solution Liver Extract Purified, 10 U S P Units per Cc** 10 cc rubber stoppered ampuls A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol, prepared by dilution of the 15 U S P unit product with water

**Solution Liver Extract Purified 15 U S P Units per Cc** 1 cc and 10 cc rubber stoppered ampuls A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol

#### THE WM S MERRILL COMPANY

**Purified Solution of Liver, 5 U S P Units per Cc** 10 cc vials A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol

**Purified Solution of Liver, 10 U S P Units per Cc** 5 cc vials A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol

#### THE NATIONAL DRUG CO

**Parenteral Solution of Liver, 5 U S P Units per Cc** 10 cc ampul vial A sterile aqueous purified solution of liver preserved with 0.5 per cent of phenol

**Parenteral Solution of Liver, 10 U S P Units per Cc** 10 cc ampul vial A sterile aqueous purified solution of liver preserved with 0.5 per cent phenol

regulate the growth of the follicles, ovulation, and corpus luteum formation.

The follicle stimulating hormone of the anterior pituitary induces growth of the graafian follicles. During this period estrogenic hormone is secreted by the follicles (probably from the cells of the theca interna), which evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification; the myometrium hypertrophies, while the endometrium changes rather rapidly to the proliferative phase. At this time the duct system of the breast develops to a varying extent. After ovulation there is a release of the luteinizing hormone of the pituitary, and the collapsed follicle becomes transformed into a corpus luteum which secretes progesterin (progesterone). In the human the corpus luteum elaborates estrogenic hormone as well. The progestational hormone induces secretory changes in the endometrium preparatory to nidation, and stimulates growth of the alveolar breast tissue. Menstruation is often claimed to result from the sudden failure of corpus luteum activity, the collapse of the endometrial structure producing the subsequent extravasation of menstrual blood. There are several discrepancies to this theory, and menstruation has not, as yet, been completely explained.

*Estrogen:* The injection of potent estrogenic substances in castrate animals will induce changes in the accessory sex organs which are typical of estrus. Long continued injections, however, induce hypertrophic then metaplastic changes in the uterus, cervix and breast. It is often considered that clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas are due to long continued estrogen secretion by the ovary.

Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. It has recently been shown that the smooth muscle of the human Fallopian tube is also responsive to estrogenic substance.

The excretion curve of estrogenic substances in the normally menstruating women is irregular and varies extremely from day to day. In general, however, there are two peaks, one at the height of follicular activity and one before menstruation. Excretion curves in ovarian disorders have not been adequately studied at the present time because of numerous technical difficulties in assays. During pregnancy large amounts of estrogens are excreted in the urine in the form of water soluble conjugate. In pregnant women these are in the form of glucuronides, and in pregnant mares in the form of sulfates. Hydrolysis of the urine, either by acid or by putrefaction, converts the conjugated estrogens into their free forms, which are more active physiologically.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estriol (trihydroxyestrin) are extracted from pregnancy urine or pla-

centas of humans while several estrogens, including estrone, equilin and hippulin are obtained from the urine of pregnant mares. Sows ovaries contain both estrone and estradiol (dihydroxyestrin), but not in sufficient quantities to make them a worthwhile source commercially. Estradiol exists in two stereoisometric forms—alpha and beta. The alpha estradiol is probably the most potent of all known estrogens, the beta form is relatively inert. Since estrogens are relatively rapidly destroyed in the animal body, several estrogen compounds which are absorbed slowly from the site of injection may be more efficient. Fatty acid esters of the estrogens (benzoate, acetate, propionate palmitate) have therefore been prepared to meet this purpose.

Estrogens may be administered by injection by emulsion with a suitable base, or by mouth. Estrone and estradiol lose considerable activity when taken orally. When estrone is administered in the form of its sulfate, it appears to retain a greater amount of its potency. Several estrogenic compounds have been prepared which lose relatively little potency when administered orally. The most promising of these at the present time is diethylstilbestrol. This is a completely synthetic product which has proved effective therapeutically by the oral route. (For further information see J. A. M. A. 107:1175 [Oct. 4] 1941.)

Besides crystalline estrogens, preparations of highly purified but noncrystalline estrogens are available. These are usually extracted from the urine of pregnant women or pregnant mares; the estrogenic activity of such extracts is due almost entirely to estrone. The Council has coined the term Solution of Estrogens for such preparations.

There has been an enormous amount of clinical research with estrogenic substances. Claims for therapeutic results have been often exaggerated and confusing. Definite and consistently reliable results have been obtained in only a relatively small number of conditions. All other indications should be considered unscientific or in the experimental stage of therapy.

Estrogens are carcinogenic in the rat, but not in the mouse. They are also carcinogenic in the rat when administered to animals which have been previously treated with a high dose of x-rays. The administration of estrogens to animals with a history of mammary cancer does not appear to increase the incidence of mammary cancer. Estrogens are therefore not considered to be carcinogenic in women who have a history of breast cancer or genital malignancy.

**Progesterone.** The hormone of the corpus luteum—induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for maturation of the ovum and the maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month, after which the placenta is responsible for its elaboration. Progesterone is not excreted as such but in the form of pregnandiol glycuronide and is found in the urine of pregnancy or during the corpus luteum phase of the normal cycle. Studies on habitual abortion have revealed that pregnandiol excreted in the urine may be

abnormally low at about the hundredth day of gestation, indicating an insufficiency of progesterone. It has been calculated that the administration of 10 mg. of progesterone daily is required to bring the pregnandiol level to normal.

A substance which has progestational activity when administered orally has recently appeared on the market. It is crystalline anhydro-hydroxy-progesterone. There is increasing evidence in the literature to indicate its therapeutic value at the present time.

Commercial preparations of progesterone are either extracts of animal ovaries, or the pure compound prepared synthetically. At one time there was considerable enthusiasm over the therapeutic use of such preparations in dysmenorrhea, menorrhagia and habitual abortion, but the volume of satisfactory evidence is too small to warrant dependence on progesterone for treatment of these conditions. The Council has not accepted progesterone or any preparation of this principle.

### *Non-Crystalline Estrogens*

**ESTROGENIC SUBSTANCES.**—*Amniotin.*—A liquid containing a highly concentrated, noncrystalline preparation of estrone (ketohydroxyestrin) together with a small varying amount of other estrogenic ketones extracted from the urine of pregnant mares.

*Actions and Uses.*—Estrogenic substances are used either orally, intravaginally or by hypodermic injection of an oil solution in a considerable variety of conditions associated with deficiency of estrogens. These include treatment of the symptoms of the menopause syndrome, natural or artificial, senile vaginitis, kraurosis vulvae, pruritis vulvae, and gonorrheal vaginitis of children. A related use is in the treatment of hypogenitalism in the female, but consideration should first be given to the possibilities of relieving such a condition by other means, such as gonadotropic therapy, which would cause the ovaries to function more normally. The use of estrogen in such conditions must be understood as substitution for ovarian function, not as stimulating such activity. Estrogens have been used in attempts to inhibit production of gonadotropic hormone by the anterior pituitary. This result requires very large doses. For a time it was thought that large doses of estrogen inhibited lactation immediately postpartum. This is doubted, but estrogenic therapy has been found helpful in relieving the engorgement of breasts especially when lactation is to be suppressed.

It has been found possible to interrupt the prolonged or excessive flowing of many women with "functional bleeding" by brief courses of intensive estrogenic therapy. This is considered safe practice only when the interval of freedom from bleeding is used to eliminate local pelvic lesions as the cause of the flowing. The subsequent administration of sequences of estrogenic substances and progesterone to reestablish cycles

of blood is a possible method of alleviating a condition which is widely believed to be a result of deficiency of one or both of the ovarian hormones.

Estrogenic materials have been reported to act together with or as a substitute for ovariectomy in the palliation of the local disease of the primary carcinoma and its metastases. The action is apparently not curative but may persist for a number of months.

*Dose*—From 200 to 2000 international units injected one or more times weekly depending on the response of the patient. After relief has been produced dosage may be lowered to a maintenance level. As much as 15000 international units per week may be required in resistant cases of kraurosis vulvae. Suppositories of estrogenic substances are valuable adjuncts in the treatment of atrophic vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of any estrogenic substance. This may be quite alarming at times and it is therefore suggested that the dose be reduced as soon as feasible.

For gonorrheal vaginitis in children from 1000 to 2000 international units daily in glycerogelatin suppositories may be required. This may be supplemented by intramuscular injection of small doses of the oil solution if necessary. Changes in the secondary sex organs may be produced by this therapy, particularly if it is too prolonged. These changes usually regress on cessation of treatment. Estrogenic products must be used with care.

Capsules of estrogenic substances 1000, 2000, 4000 or 10000 international units one or more times daily may be administered orally alone or as a supplement to parenteral therapy.

#### *Preparation—*

Urine from pregnant mares collected after the fifth month of pregnancy, is acidified with hydrochloric acid to pH 3.5 and boiled for three hours. The hydrolysed urine is extracted with ethylene dichloride and the extract evaporated to dryness. The residue is dissolved in ether, the ether solution is washed with half saturated sodium car-

The residue is further purified by high vacuum fractional distillation. The resulting residue is dissolved in sterile vegetable oil for hypodermic and oral use and incorporated in a glycerogelatin base for vaginal administration.

Estrogenic substances are assayed by a modification of the Coward and

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**GEORGE A. BREON & Co., Inc.**

**Ampul Solution of Estrogenic Substances (in oil):** 1 cc. Available as 2,000 international units per cc.; 5,000 international units per cc.; 10,000 international units per cc. of estrogenic substance.

**Ampul Solution of Estrogenic Substances (in oil):** 10 cc. rubber stoppered vials. Each cubic centimeter contains 2,000 international units of estrogenic substance.

**Solution of Estrogenic Substances (in oil) with Chlorobutanol 3%:** 10 cc. vial. Each cubic centimeter contains 10,000 international units of estrogenic substance and 30 mg of chlorobutanol as a preservative.

**THE LAKESIDE LABORATORIES, INC.**

**Ampule Solution of Estrogens (in sesame oil):** 1 cc. Available as 2,000 international units per cc., 5,000 international units per cc., 10,000 international units per cc. and 20,000 international units per cc. with 0.5 per cent chlorobutanol as preservative.

**Solution of Estrogens (in sesame oil):** 10 cc. rubber stoppered vials. Each cubic centimeter contains the equivalent of 20,000 international units of estrone and 0.5 per cent of chlorobutanol as a preservative.

**Solution of Estrogens (in sesame oil):** 15 cc. rubber stoppered vials. Available as 2,000 international units per cc. and 10,000 international units per cc. with 0.5 per cent chlorobutanol as preservative.

**Solution of Estrogens (in sesame oil):** 25 cc. rubber stoppered vials. Each cubic centimeter contains the equivalent of 2,000 international units of estrone and 0.5 per cent of chlorobutanol as a preservative.

**Tablets of Estrogens:** 1,000 international units, 2,000 international units, and 4,000 international units

**THE SMITH-DORSEY COMPANY**

**Ampul Solution of Estrogenic Substances (in peanut oil):** 1 cc. Available as 2,000 international units per cc., 5,000 international units per cc., and 10,000 international units per cc. with 0.5 per cent of chlorobutanol as a preservative

**Ampul-Vial Solution of Estrogenic Substances (in peanut oil):** 10 cc. Available as 5,000 international units, 10,000 international units and 20,000 international units of estrone with 0.5 per cent of chlorobutanol as a preservative.

**Ampul Solution of Estrogenic Substances (in sesame oil) with Benzyl Alcohol 3%:** 1 cc. Sizes containing the equivalent of 2,000 international units per cc., 5,000 international units per cc. and 10,000 international units per cc. of estrone.

**Ampul-Vial Solution of Estrogenic Substances (in sesame oil) with Benzyl Alcohol 3%:** 10 cc. Each ten centimeter contains the equivalent of 10,000 international units of estrone.

## E. R. SQUIBB & SONS

### Amniotin

**Ampules Amniotin (in corn oil):** 1 cc. containing 2,000 international units per cc., 5,000 international units per cc., 10,000 international units per cc. and 20,000 international units per cc.

**Amniotin (in corn oil):** 10 cc. vial containing 10,000 international units per cc. or 20,000 international units per cc. respectively.

**Amniotin (in corn oil):** 20 cc. vial containing 20,000 international units per cc.

**Amniotin Pessaries:** 1,000 international units, respectively.

**Capsules Amniotin:** 1,000 international units, 4,000 international units.

Trademark 315,536

**JOHN WYETH & BROTHER, INC.**

RATED

**Ampoule Solution of Estrogenic Substances (in sesame oil) with Benzyl Alcohol 3%:** 5 cc. Available as 5,000 international units and 20,000 international units. Each ampul contains 0.5 per cent benzyl alcohol.

### DIETHYLSTILBESTROL

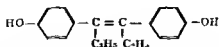
Dodds and his co-workers have prepared a series of compounds with synthetic substances, the stilbene compounds. One of these compounds can be prepared in a variety of chemicals. Its physiological actions are known to stimulate the reproductive system, stimulate the estrus, causes reddening of the skin of the plumage of the female and male, blood fat and cholesterol.

1. Dissolve 100 mg. of diethylstilbestrol in 100 cc. of acetone. Add a few drops of dry alcohol. Add a few drops of concentrated sulfuric acid. The color is produced.

2. Dissolve 100 mg. of diethylstilbestrol in 100 cc. of acetone. Add a few drops of dry alcohol. Add a few drops of concentrated sulfuric acid. The color is produced.

3. Dissolve 100 mg. of diethylstilbestrol in 100 cc. of acetone. Add a few drops of dry alcohol. Add a few drops of concentrated sulfuric acid. The color is produced.

trate animals and human beings and suppresses ovulation as well as inhibits the secretion of various factors of the anterior pituitary gland, resulting in stunting of growth, inhibition of lactation and atrophy of the gonads. It differs in its action from natural estrogens in its inability to cause the ovipositor reaction of the female bitterling and to antagonize the action of androgens on comb growth of capons. The therapeutic use has been demonstrated to be effective for all those conditions recognized to respond to the natural estrogens. Various modifications of diethylstilbestrol have been devised, such as fatty acid esters and a number of ethers, for increasing the estrogenic efficiency of this substance. These are at present the subject of clinical and physiologic investigations. Diethylstilbestrol possesses the advantage of being relatively active by mouth as well as percutaneously. The ratio of potency between oral and parenteral administration varies in the hands of different investigators from 1.2 to 1.5 in the human being as well as in rodents. In the therapeutic use of diethylstilbestrol there may be a significant incidence of side reactions, the most common of these being nausea, vomiting and headache. It has been considered that these were the result of tissue damage, but no evidence has been presented that therapeutic amounts are actually harmful to human beings and there appears to be conclusive evidence that experimentally diethylstilbestrol is not significantly more toxic than the natural estrogens. It is now considered that the unpleasant symptoms arising from diethylstilbestrol administration are systemic in origin rather than local, probably because of its rapid absorption into the blood stream, since few untoward symptoms are observed with the use of diethylstilbestrol compounds, which are slowly absorbed from the site of administration.



It may be prepared from anisaldehyde by (a) refluxing with an aqueous alcoholic solution of potassium cyanide to form anisoin, (b) reduction of the anisoin to desoxyanisoin, (c) ethylation by means of ethyl iodide and sodium ethylate to form ethyldesoxyanisoin, (d) treatment with ethyl magnesium bromide to form 3,4-dianisyl-3-hexanol, (e) dehydration to form diethylstilbestrol dimethyl ether and (f) demethylation by treatment with alcoholic potassium hydroxide to form diethylstilbestrol. The product thus obtained may be purified by recrystallization from dilute alcohol.

*Actions and Uses*—Diethylstilbestrol is used for the same conditions for which estrogenic substances are employed.

**Dosage**—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 10 mg daily by mouth although it is advised to start with smaller doses for patients who tend to develop disagreeable symptoms. Courses of therapy with

to those for natural estrogens namely familial or personal history of malignancy of the reproductive organs

### Tests and Standards—

Diethylstilbestrol occurs as a white odorless crystalline powder which melts at 169.171.5°C. When recrystallized from the various classes of solvents diethylstilbestrol forms crystals containing one molecule of solvent of crystallization which is lost with relative ease on drying at 80°C. As a consequence the commercial product when viewed under the microscope appears as a fine powder or as pitted crystals showing evidence of loss of solvent of crystallization. When diethylstilbestrol is recrystallized from dilute ethanol and observed under the polarizing microscope before drying the crystals appear as highly birefringent elongated rectangular plates exhibiting oblique extinction and positive biaxial character with many views showing an optic axis and occasionally the acute bisectrix. The optic angles are relatively large.

Diethylstilbestrol is readily soluble in ether chloroform benzene ethanol methanol and dilute sodium hydroxide soluble in vegetable

oil  
in  
alcohol  
yellow  
droplets  
free

same solvent a red colored solution is produced more concentrated solutions give a heavy red precipitate. Dissolve 10 mg of diethylstilbestrol in concentrated sulfuric acid an orange color is produced which disappears on dilution with water.

Prepare the diacetate of diethylstilbestrol by refluxing 100 mg of diethylstilbestrol with 2 cc of pyridine and 1 cc of acetic anhydride for five minutes. Dilute with 20 cc of water filter the precipitate wash several times with water and dry. Recrystallize the product from dilute ethanol and dry the melting point is from 127°C to 123.5°C. When viewed under the polarizing microscope crystals of the diacetate derivative appear as long solids exhibiting partial parallel extinction and a positive biaxial character. The refractive indices are  $n_D = 1.530$ ,  $n_F = 1.560$  and  $n_G > 1.655$ .

Transfer 0.1 gm of diethylstilbestrol to a 100 cc volumetric flask add 6 cc of 10 per cent sodium hydroxide solution and 30 cc of distilled water shake to dissolve the diethylstilbestrol then dilute to the mark with distilled water. Transfer 10 ml of the solution to a

Transfer 0.1 gm of diethylstilbestrol to a 100 cc volumetric flask add 6 cc of 10 per cent sodium hydroxide solution and 30 cc of distilled water shake to dissolve the diethylstilbestrol then dilute to the mark with distilled water. Transfer 10 ml of the solution to a

250 cc. iodine flask, fitted with an accurately ground stopper; add

place 5 cc. of 10 per cent potassium iodide solution around the stopper. Remove the stopper just enough to allow the potassium iodide solution to enter the flask, shake thoroughly, rinse the stopper and sides of the flask with distilled water and titrate with fiftieth-normal sodium thiosulfate, using starch solution as the indicator near the end of the titration. Each cubic centimeter of tenth-normal bromide-bromate solution is equivalent to 2.064 mg. of diethylstilbestrol. The diethylstilbestrol content is not less than 100 per cent.<sup>1</sup>

#### ABBOTT LABORATORIES

Ampoules Diethylstilbestrol (in sesame oil), 0.5 mg. per cc.: 1 cc.

Ampoules Diethylstilbestrol (in sesame oil), 1.0 mg. per cc.: 1 cc.

Tablets Diethylstilbestrol: 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.

Vaginal Suppositories Diethylstilbestrol: 0.1 mg. and 0.5 mg.

#### GEORGE A. BREON & COMPANY, INC.

Ampuls Diethylstilbestrol (in vegetable oil), 0.5 mg. per cc.: 1 cc.

Ampuls Diethylstilbestrol (in vegetable oil), 1.0 mg. per cc.: 1 cc.

Caplets Diethylstilbestrol: 0.2 mg., 0.5 mg. and 1 mg.

Suppositories Diethylstilbestrol: 0.5 mg.

Tablets Diethylstilbestrol: 0.2 mg., 0.5 mg. and 1.0 mg.

#### ENDO PRODUCTS, INC.

Ampules Diethylstilbestrol (in sesame oil), 0.5 mg. per cc.: 1 cc.

Ampules Diethylstilbestrol (in sesame oil), 1.0 mg. per cc.: 1 cc.

Ampules Diethylstilbestrol (in sesame oil), 2.0 mg. per cc.: 1 cc.

Ampules Diethylstilbestrol (in sesame oil) 5.0 mg. per cc.: 1 cc.

1. The nature of the reaction between bromine and diethylstilbestrol leads to complications unless the conditions of a given procedure are strictly observed. It has been found that the procedure given above tends to yield results which are somewhat higher than 100 per cent. This method of standardization must be considered tentative until more accurate analytic procedures are available.

## THE LAKESIDE LABORATORIES INC

Ampules of Diethylstilbestrol (in sesame oil), 0.1 mg per cc 1 cc containing 0.5 per cent chlorobutanol

Ampules of Diethylstilbestrol (in sesame oil), 0.5 mg per cc 1 cc containing 0.5 per cent chlorobutanol

Ampules Diethylstilbestrol (in sesame oil), 0.25 mg per cc 1 cc containing 0.5 per cent chlorobutanol

Ampules Diethylstilbestrol (in sesame oil), 1.0 mg per cc 1 cc containing 0.5 per cent chlorobutanol

Ampules Diethylstilbestrol (in sesame oil), 2.0 mg per cc 1 cc containing 0.5 per cent chlorobutanol

Ampules Diethylstilbestrol (in sesame oil), 5.0 mg per cc 1 cc containing 0.5 per cent chlorobutanol

Tablets Diethylstilbestrol 0.25 mg 0.1 mg 0.5 mg 1.0 mg 2.0 mg and 5.0 mg

## LEDERLE LABORATORIES, INC

Ampuls Diethylstilbestrol (in sesame oil), 0.5 mg per 0.5 cc 0.5 cc

Ampuls Diethylstilbestrol (in sesame oil), 1 mg per cc 1 cc

Capsules Diethylstilbestrol 0.1 mg 0.5 mg and 1.0 mg

## ELI LILLY &amp; COMPANY

Ampoules Diethylstilbestrol (in cottonseed oil) 0.25 mg per cc 1 cc

Ampoules Diethylstilbestrol (in cottonseed oil) 0.5 mg per cc 1 cc

Ampoules Diethylstilbestrol (in cottonseed oil), 1 mg per cc 1 cc

Ampoules Diethylstilbestrol (in cottonseed oil) 5 mg per cc 1 cc

Suppositories Diethylstilbestrol 0.1 and 0.5 mg

Tablets Diethylstilbestrol 0.1 mg 0.25 mg 0.5 mg 1 mg and 5 mg

## THE WM S MERRELL COMPANY

Diethylstilbestrol (in corn oil) 1 mg per cc 20 cc vial containing 0.5 per cent chlorobutanol

Tablets Diethylstilbestrol 1.0 mg and 0.2 mg

## THE SMITH DORSEY COMPANY

Ampuls Diethylstilbestrol (in peanut oil) 0.5 mg per cc 1 cc

Ampuls Diethylstilbestrol (in peanut oil), 1 mg. per cc.: 1 cc.

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 1 mg.

#### **E. R. SQUIBB & SONS**

Ampuls Diethylstilbestrol (in corn oil), 0.2 mg. per cc.: 1 cc.

Ampuls Diethylstilbestrol (in corn oil), 0.5 mg. per cc.: 1 cc.

Ampuls Diethylstilbestrol (in corn oil), 1.0 mg. per cc.: 1 cc.

Ampuls Diethylstilbestrol (in corn oil), 50 mg. per cc.: 1 cc.

Diethylstilbestrol Pessaries: 0.1 mg. and 0.5 mg.

Tablets Diethylstilbestrol: 0.25 mg., 0.1 mg., 0.5 mg., 10 mg. and 50 mg.

#### **FREDERICK STEARNS & COMPANY**

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 10 mg.

#### **THE UPJOHN COMPANY**

Ampoules Sterile Solution Diethylstilbestrol (in vegetable oil), 0.5 mg. per cc.: 1 cc.

Ampoules Sterile Solution Diethylstilbestrol (in vegetable oil), 1.0 mg. per cc.: 1 cc.

Perles Diethylstilbestrol: 0.1 mg., 0.5 mg. and 10 mg.

Perles Diethylstilbestrol (in oil): 0.25 mg.

Suppositories Diethylstilbestrol (Juvenile Size): 0.1 mg.

Suppositories Diethylstilbestrol (Adult Size): 0.5 mg.

#### **THE WARREN-TEED PRODUCTS CO.**

Ampuls Sterilized Solution Diethylstilbestrol (in sesame oil), 1 mg. per cc.: 1 cc.

Sterilized Solution Diethylstilbestrol (in sesame oil), 1 mg. per cc.: 15 cc. containing 0.5 per cent chlorobutanol.

Tablets Diethylstilbestrol: 0.5 mg. and 1 mg.

#### **WINTHROP CHEMICAL COMPANY, INC.**

Ampuls Diethylstilbestrol (in sesame oil), 0.5 mg. per cc.: 1 cc.

Ampuls Diethylstilbestrol (in sesame oil), 1 mg. per cc.: 1 cc.

Suppositories Diethylstilbestrol: 0.1 mg. and 0.5 mg.

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg., 1 mg. and 5 mg.

JOHN WYETH & BROTHER DIVISION WYETH INCORPORATED

Ampoules Diethylstilbestrol in corn oil), 0.5 mg per cc 1 cc

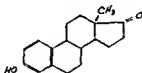
Ampoules Diethylstilbestrol (in corn oil), 1.0 mg per cc 1 cc

Suppositories Diethylstilbestrol 0.1 mg and 0.5 mg

Tablets Diethylstilbestrol 0.1 mg, 0.5 mg and 0.25 mg

### Crystalline Estrogens

ESTRONE—Theelin— $C_{18}H_{18}O_2$ —U S P



For description and standards see the U S Pharmacopeia under Estronum

*Actions and Uses*—Estrone is used for the same conditions for which estrogen substances are employed

*Dosage*—In disturbances of the menopause 0.2 mg (2000 I U) to 1.0 mg (10000 I U) injected intramuscularly one or more times weekly depending on the response of the patient. After producing relief dosage may be lowered to a maintenance level. As much as 50 mg (50000 I U) per week may be required in resistant cases of kraurosis vulvae. Estrone suppositories are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of estrone. This may be quite alarming at times and it is therefore advisable to reduce the dose of estrone as soon as feasible.

For gonorrheal vaginitis in children from 0.02 to 0.2 mg (200 to 2000 international units) in glycerogelatin suppositories daily or as required. This may be supplemented by intramuscular injection of small doses of the oil solution if necessary. Changes in the secondary sex organs may be produced by this therapy particularly if it is too prolonged. These changes usually regress on cessation of treatment.

Estrone is effective by mouth if the dosage is adequate.

Estrone is manufactured under license from St. Louis University under U S patents 1967350 and 1967351 (July 24 1934 expire 1951).



## ABBOTT LABORATORIES

## Estrone Crystals.

**Ampoules Estrone (in sesame oil):** 0.2 mg. in 1 cc. (2,000 international units); 0.5 mg. in 1 cc. (5,000 international units), and 1 mg. in 1 cc. (10,000 international units).

**Ampoules Estrone Suspension:** 2 mg. in 1 cc. (20,000 international units). Each cubic centimeter contains estrone crystals 2 mg. in aqueous suspension with gum acacia.

**Vaginal Suppositories Estrone:** 0.2 mg. in a glycerogelatin base.

## ELI LILLY AND COMPANY

**Ampules Estrone (in cotton seed oil):** 0.1 mg. in 1 cc. (1,000 international units); 0.2 mg. in 1 cc. (2,000 international units); 0.5 mg. in 1 cc. (5,000 international units), and 1 mg. in 1 cc. (10,000 international units).

**Vaginal Suppositories Estrone:** 0.2 mg. (2,000 international units) in a glycerin base.

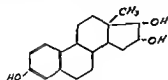
## PARKE, DAVIS &amp; COMPANY

**Ampoules Theelin (in peanut oil):** 0.1 mg. in 1 cc. (1,000 international units), 0.2 mg. in 1 cc. (2,000 international units); 0.5 mg. in 1 cc. (5,000 international units), and 1 mg. in 1 cc. (10,000 international units).

**Ampoules Theelin Aqueous Suspension:** 2 mg. in 1 cc. (20,000 international units).

**Vaginal Suppositories Theelin:** 0.2 mg. (2,000 international units) in glycerogelatin base.

**ESTRIOL.**—Theelol— $C_{27}H_{48}O_4$ .—3,16,17-trihydroxy  $\Delta$  1,3,5—estratriene. A crystalline estrogenic steroid isolated from the urine of pregnancy. Estriol is much less actively estrogenic than estrone when injected. The terms Estriol and Theelol are nonproprietary synonyms.



**Actions and Uses.**—Estriol (theelol) is used orally for the same conditions for which estrogenic substances are employed.

**Dosage.**—Orally from 0.06 to 0.12 mg. from one to four times a day, alone or as supplement to parenteral therapy.

*Tests and Standards—*

approximately 0.04 Gm of estriol accurately weighed to a 1 cc microvolumetric flask fill to the mark with freshly distilled dioxane and determine the optical rotation after the U S P XI method page 459 using a 2 dcm microtube The specific rotation  $[\alpha]_{\text{D}}^{25}$  is + 58 degrees

(± 5 degrees)

Dissolve approximately 0.06 Gm of estriol accurately weighed in a pyridine (6 cc) and acetic anhydride (2 cc) mixture (3:1) and heat under a micro reflux condenser for twenty four hours at 95 C Transfer the solution to a 250 cc flask containing 100 cc of ice-cold water and titrate with 0.1 normal sodium hydroxide the acetic acid value is not more than 129 nor less than 121 equivalent to three

phosphorus pentoxide the melting point of the triscetate is 126 C (± 1 degree)

Transfer approximately 2 mg of estriol accurately weighed to a previously weighed microplatinum boat add 0.05 cc of sulfuric acid (1:3) incinerate in the muffle oven no residue should remain Micro carbon and hydrogen analysis according to Pregl's method gives a carbon content of not more than 75.2 per cent not less than 74.6 per cent and a hydrogen content of not more than 8.7 per cent nor less than 8.0 per cent

Estriol crystals exhibit a reddish fluorescence under filtered ultra violet light

The dosage forms of brands of estriol are biologically assayed the assay being under control of the St. Louis University committee

Estriol is manufactured under license from St. Louis University under U S patents 1967350 and 1967351 (July 24, 1934 expire 1951)

**ABBOTT LABORATORIES****Estriol Crystals**

Capsules Estriol 0.06 mg 0.12 mg and 0.24 mg

**ELI LILLY AND COMPANY**

Pulvules Estriol 0.06 mg, 0.12 mg and 0.24 mg

**PARKE, DAVIS & COMPANY**

Kapskals Theciol 0.06 mg 0.12 mg and 0.24 mg

## Pancreas

The pancreas is a gland having, in general, two functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the blood a hormone, insulin, which regulates the process of carbohydrate metabolism.

When insulin secretion is deficient, or possibly when there is an overproduction of sugar due to other causes, diabetes develops. In this disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first and last stages in the metabolism of sugar, as revealed, respectively, by failure of glycogen to be deposited in the liver and by failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism may be accompanied by an accumulation of ketone substances (acetone, acetoacetic and oxybutyric acids) with resultant acidosis and, later, coma.

of sugar, increased storage as glycogen in the liver and possibly in the muscles is a factor in the result. When the percentage of blood sugar falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar in the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit will on an average promote the metabolism of approximately 15 Gm. of dextrose. The physician may, therefore, gauge his insulin dose with some precision. To do so, he must know how much dextrose the patient will derive from his food and metabolism, and how much insulin the patient himself can provide from his insulin-making tissues. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. In any case, insulin injections must be made at regular intervals and must be supplemented by accurately weighed diets of known composition.

When properly employed, insulin is a specific in the treatment of diabetic coma and acidosis. It is of pronounced value

in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's antidiabetic function. In the severer cases the evidence now available is against such an assumption. In the milder cases in which insulin has been used the evidence is difficult of interpretation because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation and exercise alone.

*Oral Administration of Pancreatic Preparations*—In diabetes reliance on the oral administration of the pancreatic preparations thus far prepared has no justification and such practice merits the most vigorous condemnation. Many reputed anti-diabetic pancreatic preparations are on the market with claims that they are effective if taken by mouth. The most widely heralded of them have been subjected to the scrutiny of clinical tests controlled with simultaneous laboratory investigation. None of these thus tested has shown any effect on blood sugar or glycosuria. Completely negative results were obtained when these preparations were given in the doses recommended by their exploiters as well as in doses twenty times as large. The claim that such preparations exert, in some mysterious manner, a rejuvenating or stimulating action on the diseased pancreas is based on uncontrolled clinical observation.

**INSULIN INJECTION**—Insulin—Insulin Hydrochloride—An acidified aqueous solution of the active principle of the pancreas which affects the metabolism of glucose. Insulin Injection when assayed as directed shall possess a potency of not less than 95 per cent and not more than 105 per cent of the potency stated on the label and the potency shall be expressed in U. S. P. Insulin Units which are equivalent in potency to the Unit declared on the label of the container of the U. S. P. Zinc-Insulin Crystals Reference Standard.

Insulin Injection is so standardized that each cc contains either 20, 40, 80 or 100 U. S. P. Insulin Units.

The label of the Insulin Injection container must state the potency in U. S. P. Insulin Units per cc and the outside labeling of each retail package shall also state a date of expiration which must not be later than two years after the date of its removal for distribution from the manufacturer's place of storage the temperature of which shall be above 0° C but shall not exceed 15° C.

Insulin Injection must contain from 0.1 to 0.25 per cent (w/v) of either phenol or cresol. The solution must contain from 1.4 to 1.8 per cent (w/v) of glycerin. U. S. P.

For description and standards see the U. S. Pharmacopeia under *Injectio Insulin*.

*Actions and Uses.*—Insulin lowers the blood sugar in normal rabbits causing characteristic symptoms when a low level is reached, which symptoms are overcome by the administration of dextrose. It prevents the hyperglycemia due to piqure, asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. It causes glycogen to be deposited in the liver of diabetic animals fed with carbohydrates, and raises the respiratory quotient of such animals. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine. It has been demonstrated that the administration of insulin to diabetic dogs and to man in severe cases of diabetes mellitus restores temporarily to the body the impaired ability to oxidize carbohydrate, and that glycogen is again stored in the liver. If a suitable dose of insulin is administered at suitable intervals to a person suffering from diabetes mellitus, the blood sugar is maintained at a normal level and the urine remains free of sugar; fat is also burned and as a result, ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

The administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by dietetic treatment. In such cases, with proper regulation of the diet, insulin should be administered in such amounts as to prevent glycosuria and a too great hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body power of utilizing carbohydrate returns toward normal.

Overdosage of insulin is followed by the development of serious symptoms which demand immediate treatment. The patient complains of weakness and fatigue and a feeling of nervousness or tremulousness. This is followed by profuse sweating, which is the most characteristic sign of overdosage. There is sometimes pallor or flushing. In the more severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate, such as orange juice, by mouth or stomach tube, or, if the patient is comatose, by the intravenous injection of from 5 to 20 grams of pure dextrose in a 5 to 50 per cent sterile solution. Although symptoms of hypoglycemia usually develop gradually, the onset in occasional cases may be sudden. In view of this, ambulant patients should be instructed to carry, for immediate use, soluble carbohydrate in the form of powdered dextrose or an orange. Physicians treating patients with insulin should be impressed with the necessity of having adequate supplies of sterile solution of dextrose at hand. In case of emergency when sterile solution of dextrose is not available, a subcutaneous injection of 0.3 cc. to 0.6 cc. of 1 in 1,000 solution of epinephrine may be employed, but this must always be followed by carbohydrates by mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there is usually very little in the diabetic organism.

Epinephrine should never be employed when the hypoglycemia follows excessive exercise, vomiting or the omission of meals.

Insulin has been used in the treatment of non diabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary in avoiding symptoms of hypoglycemia.

Insulin has been suggested and used rather extensively in psychopathic hospitals for the purpose of producing hypo-

suitable solutions of dextrose for interrupting the hypoglycemic state which is artificially created in these individuals by the administration of insulin.

**Dosage**—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually thirty minutes before meals. There is no average dose of insulin for diabetics, each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate dextrose tolerance to provide him with a diet sufficient for light work. The dose depends upon the amount of dextrose in such a diet as he is unable to metabolize, i. e., the total dextrose minus the dextrose excretion. A convenient formula

is 
$$\frac{\text{Average grams of d glucose excreted}}{15} = \text{sufficient units of insulin}$$

to render most patients aglycosuric. Usually the daily dose is administered in two equal portions, one before breakfast and

the fasting blood sugar normal, but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose gradually increased until therapeutic results are obtained. Complications, such as infections, may reduce the dextrose tolerance, thus necessitating an increase of insulin dosage.

In cases of coma or severe acidosis an initial dose of 30-60 units may be given (in coma one half the amount intravenously and one half subcutaneously) followed at  $\frac{1}{2}$  to 3 hour intervals by doses of 20 units or more subcutaneously. Some physicians administer 1 Gm. of dextrose for each unit of insulin used. The patient should never become hypoglycemic. Examine the urine hourly for dextrose. If urine becomes sugar free more dextrose must be given. More than 150 units of insulin in twelve hours is rarely needed. Young children with diabetes of recent onset usually require smaller doses and seldom more than 80 units in the first 12 hours.

the solution through a Whatman filter No. 1 (7 cm.), wash with 10 cc hydrogen sulfide saturated water containing 5 cc of 90 per cent formic acid in 1 liter. After the filter is dry, elute the zinc with approximately 15 cc. 1 normal hydrochloric acid and transfer into a flat bottom Nessler tube. Add 2 cc. of 5 normal sodium hydroxide and fill up to 20 cc. Add 2 drops of 2 per cent potassium ferrocyanide, and compare with standards containing 0.05 mg to 0.1 mg zinc (nephelometrically): One cc. of protamine zinc insulin containing 40 units per 1 cc. should yield the equivalent of not less than 0.03 mg., nor more than 0.10 mg. of zinc. The zinc standard is made by dissolving 1 Gm of pure zinc in concentrated hydrochloric acid, diluting it to 1 liter.

Patents and trademarks—See Insulin, N. N. R. Additional patents applied for.

### ELI LILLY AND COMPANY

**Protamine, Zinc and Iletin, 40 Units:** 10 cc. vials Each 1 cc. contains 40 units of protamine zinc insulin.

**Protamine, Zinc and Iletin, 80 Units:** 10 cc. vials Each 1 cc. contains 80 units of protamine zinc insulin

### SHARP & DOHME, INC.

**Protamine Zinc Insulin, 40 Units:** 10 cc vials Each 1 cc contains 40 units of protamine zinc insulin Contains disodium acid phosphate 0.2 per cent, phenol 0.25 per cent as a preservative, and glycerin 1.6 per cent for isotonicity

**Protamine Zinc Insulin, 80 Units:** 10 cc vials. Each 1 cc. contains 80 units of protamine zinc insulin. Contains disodium acid phosphate 0.2 per cent, phenol 0.25 per cent as a preservative, and glycerin 1.6 per cent for isotonicity.

### E. R. SQUIBB & SONS

**Protamine Zinc Insulin, 40 Units:** 10 cc vials Each 1 cc contains 40 units of protamine zinc insulin

**Protamine Zinc Insulin, 80 Units:** 10 cc vials Each 1 cc contains 80 units of protamine zinc insulin

**ZINC INSULIN CRYSTALS.**—Zinc insulin crystals occur as a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent), which is chemically combined with the active principle. The presence of zinc or some other heavy metal such as nickel or cobalt is essential because only in the presence of traces of such elements has the active antidiabetic principle been prepared in a pure crystalline form. Each milligram of the crystals is equivalent to approximately 22 units of insulin. The product is marketed in the form of crystalline zinc-insulin injection

Zinc insulin crystals occur as small, colorless, rounded, untwinned uniaxial, rhombohedral crystals, possessing a negative optic sign, parallel or zero extinction between crossed Nicols and a mean index of refrac

tion for lithium light of  $1.535 \pm 0.002$  with a birefringence of 0.005. It is sparingly soluble in water, insoluble in alcohol, chloroform and ether but soluble in dilute acid and dilute alkali. The isoelectric point of zinc insulin crystals is about 5.3. The crystals are stable if kept at a low temperature.

Transfer about 20 mg of zinc insulin crystals to a platinum boat, weigh the boat and its contents within a weighing "pig," place the boat in a vacuum desiccator over phosphorus pentoxide and dry to constant weight using the weighing "pig" to prevent the absorption of water during weighing. The loss in weight does not exceed 7.0 per cent. In the following quantitative determinations it is more convenient to weigh the zinc insulin crystals directly and to calculate the results to a dry basis rather than attempt to weigh the extremely hygroscopic dry material.

Dissolve 50 mg of zinc insulin crystals in 5 cc of water by the addition of sufficient tenth normal hydrochloric acid to effect solution, transfer to a centrifuge tube and add 2 cc of 10 per cent trichloroacetic acid with shaking, let stand ten minutes and centrifuge; decant into a 10 cc volumetric flask, add 2 cc of Nessler's reagent and make up to volume, allow to stand five minutes, transfer to a colorimeter and compare with a standard made up similarly and containing 0.055 mg of ammonium sulfate; the color does not exceed that of the standard solution.

Transfer 18 mg of zinc insulin crystals to a 100 cc volumetric flask, add 2 cc of tenth normal hydrochloric acid, dilute to the mark with distilled water and shake to dissolve the crystals. Transfer 10.0 cc of this solution to a separator, add about 20 cc water, 10 cc chloroform and 2 cc dithizon reagent (prepared by dissolving 15 mg dithizon in 100 cc redistilled chloroform). Make the solution alkaline by the addition of ammonia water and shake until the chloroform layer is colored a clean flask and repeat portions of chloroform to hizon reagent until the point the aqueous layer chloroform extracts to a clean separator and extract twice with 15 cc portions of 0.02 normal

### CRYSTALLINE ZINC INSULIN INJECTION—A

solution of zinc insulin crystals, a preparation containing the active antidiabetic principle of the pancreas, combined with a small amount of zinc (not less than 0.2 and not more than 0.40 mg per thousand units of active principle in the solution).



*Actions and Uses.*—Crystalline zinc insulin injection may be used in the treatment of diabetes mellitus when regulation of diet has been unsatisfactory in control of the disease. Because of its chemical purity, solution of zinc insulin crystals is especially indicated for patients who may be expected to exhibit allergic reactions to insulin. Experience has indicated that the occurrence of such reactions may thus be avoided or minimized. Although early clinical observations indicated that the action of crystalline zinc insulin injection as compared with that of insulin may be slightly delayed and somewhat prolonged, further clinical experience has shown, however, that in patients under careful observation crystalline zinc insulin injection and insulin may be used interchangeably.

*Dosage.*—The potency of crystalline zinc insulin injection is measured in terms of standard units of insulin. The general principles underlying its administration are the same as those covering the use of insulin, and under ordinary circumstances the two solutions may be regarded as interchangeable. The crystalline zinc insulin injection is usually best administered subcutaneously fifteen to thirty minutes before a meal. The time and number of the doses and the amount of solution must be determined by the need of the individual patient, each of whom requires accurate dietary regulation and meticulous clinical study.

Marketed solutions of zinc insulin crystals are water clear and contain from 1.4 to 1.8 per cent w/v of glycerin for isotonicity; 0.1 to 0.25 per cent w/v of phenol or tricresol as a preservative; and sufficient zinc ions to form a complex with the insulin. The solutions are stable at room temperature and do not exceed room temperature. Crystalline zinc insulin injection meets the requirements for identity and purity provided in the U. S. P. XII under *Injectio Insulini*.

Solutions c

temperature does not exceed room temperature. Crystalline zinc insulin injection meets the requirements for identity and purity provided in the U. S. P. XII under *Injectio Insulini*.

## Parathyroid

Parathyroid preparations for oral administration are made from the dried gland and for subcutaneous administration by extraction of the gland by suitable solvents and subsequent purification of the product. The reports of success after oral therapy lack any conclusive evidence that this was dependent upon the use of the gland. No proof has been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations taken by mouth. To ascribe to the oral administration of parathyroid preparations improvement in conditions that are not definitely known to depend upon parathyroid disease, or deficiency, is illogical and misleading. In consideration of the accumulated evidence of the ineffectiveness of oral therapy with parathyroid,

preparations of parathyroid designed for oral administration are not accepted for inclusion in this book

Preparations which have a powerful influence on calcium metabolism may be made from the parathyroids of the ox. If this substance is injected intramuscularly or subcutaneously the calcium concentration of the serum of animals deprived of their parathyroid glands can be raised and maintained at a normal limit. By repeated doses it may be raised far beyond this, either in parathyroidectomized or in normal animals and unless the dosage is carefully regulated, death may ensue. The preparations can be standardized according to their activity in raising the calcium concentration in parathyroidectomized animals or in normal animals. On subcutaneous and intramuscular injections the plasma calcium begins to rise in about 4 hours, reaches its maximum in from 12 to 18 hours and returns to the previous level in from 20 to 24 hours. Associated with the rise in serum calcium is an increased urinary excretion of calcium and inorganic phosphate and a decrease in the serum content of the latter. An immunity or tolerance to the hormone is induced by repeated administration. Treatment by these parathyroid preparations has been shown to be of value in tetania parathyreopriva. In infantile tetany their employment should be confined to those cases in which a reduction in the level of serum calcium has been demonstrated and would appear to be a temporary expedient until other measures have an opportunity to combat the fundamental underlying condition. In gastric tetany the calcium of the serum is normal and it has not been demonstrated that this condition can be affected beneficially by parathyroid therapy. The available clinical or scientific evidence does not permit an estimate of the ultimate usefulness of the parathyroid preparation in other conditions. The danger of hypercalcemia which is easily induced by overdosage and which is associated with grave manifestations makes it desirable that the clinical use of parathyroid preparations should be controlled by blood serum calcium determinations or by application of the Sulkowitch test for calcium in the urine. The normal concentration of calcium in the serum is approximately 10 mgm of calcium per 100 ml of serum. Doses of 10 to 12 mgm of calcium are considered safe. Larger doses may be dangerous and produce troublesome effects. Continued use of the hormone, with almost complete loss of therapeutic effect. For this reason, other substances such as dihydrotachysterol or calciferol, which cause elevation of serum calcium should be substituted as soon as possible.

**PARATHYROID** . . . . . fact  
—Solution of . . . . . for  
injection of the . . . . . the  
parathyroid gla . . . . . the  
symptoms of parathyroid tetany and of increasing the calcium

content of the blood serum in man and other animals. It is obtained from the fresh parathyroid glands of healthy domesticated animals used for food by man, the animal source of each preparation being stated. The parathyroid glands must be removed from the animals immediately after slaughtering, and then extracted at once or kept frozen until extracted. The glands are freed from gross fat and connective tissue, ground, extracted, and the extract purified to make it suitable for parenteral administration. The injection is then adjusted to the proper potency.

"One cc. of Parathyroid Injection possesses a potency of not less than 100 U. S. P. parathyroid units, each unit representing one one-hundredth of the amount required to raise the calcium content of 100 cc. of the blood serum of normal dogs 1 mg. within sixteen to eighteen hours after administration" *U. S. P.*

For description and standards see the U. S. Pharmacopeia under *Injectio Parathyroidi*.

*Actions and Uses* (See preceding article, Parathyroid).

*Dosage.*—In severe seizures of acute proved parathyroid tetany such as may follow removal of the parathyroid glands during thyroidectomy a dose of 100-300 units (10-30 cc.) may be necessary. Beneficial effect, as evidenced by an elevation in the serum calcium, is usually apparent within a few hours and reaches a maximum in 8-18 hours. For maintenance of the level of serum calcium the average adult dose is 0.2-0.4 cc (20-40 units) every 12 hours. The continuance and regulation of such dosage must be controlled by determinations of the level of the serum calcium. In the treatment of chronic parathyroid tetany parathyroid injection is less effective than dihydrotachysterol or vitamin D<sub>2</sub> and is usually unnecessary if one of these substances can be provided in appropriate amounts. In infants the use of parathyroid injection should be more cautious and even in those cases where a reduction of serum calcium has been demonstrated the initial dosage should not exceed 0.1-0.2 cc. (10-20 units).

#### **ELI LILLY AND COMPANY**

**Ampules Solution Parathyroid Extract: 1 cc. (100 units)**

**Solution Parathyroid Extract: 5 cc. vials** Each 1 cc. contains 100 units

#### **PARKE, DAVIS & COMPANY**

**Paroidin.**

**Solution Paroidin: 5 cc vials.** Each 1 cc. contains 100 units

U S patent 1,890,851 (Dec 13, 1932, expires 1949) U S trademark

#### **E. R. SQUIBB & SONS**

**Solution Parathyroid Hormone: 5 cc. vials** Each cc. contains 100 units

## Pituitary

*Posterior Lobe*—The posterior lobe of the pituitary gland yields on extraction substances having a marked effect on plain muscle, especially that of the blood vessels and the uterus. The intravenous or intramuscular injection of preparations of the posterior lobe is sometimes followed by an increase in blood pressure which is maintained over a considerable period of time. Injection of subsequent doses in such cases is followed by a similar effect unless repeated too soon after the first injection when a fall in pressure may occur. The increase in pressure is due to an action on the smooth muscle of the vessels. In a considerable number of individuals the increase in blood pressure may be very slight and in some instances instead of an increase a definite lowering of the blood pressure may follow the injection of pituitary preparations. The heart is not stimulated in any case and may be depressed either through the vagus response to a high blood pressure or by a direct action on the heart muscle itself or through impairment of its nutrition because of constriction of the coronary vessels. The tone of the intestinal tract may be markedly increased by direct action on the muscular coat. The administration of extracts usually retards the secretion of urine to a marked degree during the first hour and a half and sometimes longer. There is some experimental evidence to show that the absorption of water from the gastrointestinal tract is delayed thereby lessening the water available for secretion. However, the antidiuretic action may be due to increased reabsorption of water from the kidney tubules into the blood. The bladder musculature is stimulated especially when it has been previously in an atonic condition. Posterior pituitary extract does not increase the formation of milk but may cause a temporary acceleration of the output. The extract of the posterior lobe causes a marked contraction of the uterus by a direct stimulating action on the muscle. This occurs especially in pregnant and to a less extent in nonpregnant animals.

Solutions prepared from the posterior lobe injected intramuscularly are employed against uterine atony and in postpartum as well as in other forms of uterine hemorrhage. They should not be injected during the first stage of labor because if the cervix be not fully dilated energetic contractions may cause rupture of the uterus or extensive laceration of the soft tissue. Most authorities also advise against the use of pituitary preparations in the second stage of labor.

Pituitary solutions may be useful in intestinal paresis whether following abdominal operations or complicating infectious diseases. The extracts are also extensively used in diabetes insipidus in which they reduce greatly the volume of urine excreted. For this purpose they are injected once or twice daily. The extracts should always be injected hypodermically or intramuscularly although some activity appears when they are applied to the nasal mucous membrane. The extract of the

posterior lobe of the pituitary gland has been fractionated: one product (pitocin) acting on the uterus and a second product (pitressin) producing the characteristic effect of the original solution on the blood vessels, intestine and urinary secretion.

*Anterior Lobe.*—Hyperactivity of the anterior lobe is believed to produce gigantism and acromegaly, for clinically both conditions have been accompanied by tumors of the pituitary. Evidence has accumulated which indicates that the hormone of the anterior lobe is essential to normal growth and the development of the ovaries and testes, but that it may have nothing to do with some of the other disturbances formerly attributed to abnormal functioning of the pituitary, as a considerable number of cases of Fröhlich's syndrome have come to autopsy in which the pituitary has been histologically normal. It is also claimed that extirpation of the hypophysis in adult dogs and white rats without injury to the hypothalamus does not produce dystrophia adiposogenitalis. Extirpation in immature animals is followed by cessation of growth and sexual development, a condition which has been corrected in white rats by daily transplants of the anterior lobe of the pituitary or by daily injections of appropriate amounts of the fresh extract of the anterior lobe of bovine glands.

Present evidence would seem to indicate that a number of factors are concerned in the action of extracts of the anterior lobe: (1) a growth factor concerned with the development of the body; (2) a factor which stimulates the growth and maturation of the ovarian follicle, which in turn bring on the changes characteristic of estrus; (3) a factor which causes luteinization of the ovarian follicles; (4) a factor which is necessary for normal thyroid development and function and which, if present in excess, produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea pig; (5) a factor which produces lactation in mammals, and possibly plays a part in mammary gland proliferation; it also induces a secretion of crop milk in pigeons; (6) a diabetogenic principle which decreases the hypoglycemic response to insulin and which experimentally damages the cells of the islets of Langerhans thus producing the diabetic syndrome; and (7) a ketogenic principle, apparently distinct from the diabetogenic factor, which increases the ketone content of the blood in rabbits and rats. In addition to the above enumerated factors, the existence of which seems to be clearly established, experimental evidence has been offered indicating the presence of other principles; among these is one which stimulates the adrenal cortex known as the adrenotropic hormone.

A gonadotropic substance which forms the basis of pregnancy tests occurs in large amounts in the urine of pregnancy. Although this substance was originally considered to come from the anterior pituitary gland, the placenta which also yields it in large amounts seems to be a more probable source. It is predominantly luteinizing in action in contrast to the anterior lobe

principle found in the urine at the menopause and after castration which produces a greater degree of follicular stimulation

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe

**AMPOULES OF PITOCIN**—An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland (alphahypophamine) containing less than  $\frac{1}{2}$  unit of pressor activity per cubic centimeter. Five tenths per cent of chlorbutanol is used as a preservative. It is standardized by the U S P method for posterior pituitary each cubic centimeter containing 10 units. Pitocin therefore has an activity on the uterus equal to that of the U S P solution of pituitary

*Actions and Uses*—Pitocin is used to stimulate uterine contractions in obstetrical practice

The use of the product may be particularly indicated in those cases in which increase of blood pressure is undesirable. Its use is contraindicated in contracted pelvis and in incomplete dilatation of the cervix. (See preceding article Pituitary)

*Dosage*—From 0.3 cc to 1 cc intramuscularly. If used before delivery is completed small doses are used repeated if necessary in twenty to thirty minutes

PARKE DAVIS & COMPANY

Pitocin bulk

U S patent 1960493 (May 29 1934 exp res 1951) U S trademark 254956

Ampoules of Pitocin 0.5 cc and 1 cc

...

..

exhibited by 0.5 mg of Posterior Pituitary U S P Reference Standard U S P)

*Actions and Uses*—Pitressin is used for raising the blood pressure for increasing the muscular activity of the bladder and intestinal tract also for antidiuretic effect in diabetes insipidus. (See preceding article Pituitary)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product

may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

*Dosage.*—From 0.3 to 1 cc. intramuscularly, repeated as may be indicated.

#### PARKE, DAVIS & COMPANY

**Pitressin:** bulk

U. S. patent 1,960,493 (May 29, 1934, expires 1951) U. S. trademark 254,507.

**Ampoules of Pitressin:** 0.5 cc. and 1 cc.

**PITRESSIN TANNATE IN OIL.**—A suspension in vegetable oil of a water insoluble tannate of the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland (beta-hypophamine) standardized to contain five pressor units in each cubic centimeter (one unit representing the pressor activity exhibited by 0.5 mg. of standard powdered pituitary U. S. P.). It is standardized by the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* 2:120 [Nov.] 1916).

*Actions and Uses.*—Pitressin tannate in oil is recommended for use where the prolonged action of pitressin is desired, particularly for the treatment of patients suffering from diabetes insipidus.

*Dosage.*—From 0.3 to 1 cc. (3 to 5 pressor units) intramuscularly, *never intravenously*, at intervals of from thirty-six to forty-eight hours.

#### PARKE, DAVIS & COMPANY

**Ampoules Pitressin Tannate in Oil:** 1 cc. Each cubic centimeter contains pitressin tannate equivalent to 5 pressor units, in peanut oil suspension.

U. S. patent 1,960,493 (May 29, 1934, expires 1951) U. S. trademark 254,507.

**POSTERIOR PITUITARY INJECTION.**—Liquor Pituitarii Posterioris U. S. P. XL.—Solution of Pituitary.—“A sterile solution in water for injection of the water-soluble principle or principles from the fresh posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The pituitary body must have been removed from the animal immediately after slaughtering, and then dried or extracted at once or kept frozen until extracted. The potency of Posterior Pituitary Injection shall be such that 0.1 cc. of the Injection shall possess an activity equivalent to one U. S. P. Posterior Pituitary Unit” U. S. P.

For description and standards see the U. S. Pharmacopeia under *Injectio Pituitarii Posterioris*.

*Actions and Uses.*—See preceding article, Pituitary.

*Dose*—For medicinal cases from 0.2 to 1 cc in surgical cases from 1 to 2 cc preferably by deep intramuscular injection or subcutaneously

**ABBOTT LABORATORIES**

Ampoules Posterior Pituitary Solution 0.5 cc and 1 cc

**THE ARMOUR LABORATORIES**

Pituitary Liquid

**INDO PRODUCTS, INC.**

Ampoules Solution of Posterior Pituitary 0.5 cc and 1 cc

**THE LAKESIDE LABORATORIES, INC.**

Ampules Pituitary Solution 0.5 cc and 1 cc

Pituitary Solution 10 cc and 30 cc vials

**ELLI LILLY AND COMPANY**

Ampoules Pituitary Extract 0.5 cc and 1 cc

**THE W. S. MERRELL COMPANY**

Pituitary Extract

**PARKE DAVIS & COMPANY**

Pituitrin

Ampoules Pituitrin 0.5 cc and 1 cc

U. S. trademark 76722

**E. R. SQUIBB & SONS**

Ampoules Posterior Pituitary Injection 0.5 cc and 1 cc

**THE LIJOHN COMPANY**

Ampoules Solution Pituitary Extract 0.5 cc and 1 cc

Solution Pituitary Extract 20 cc vials

**U. S. STANDARD PRODUCTS CO.**

Ampuls Pituitary Solution 0.5 cc and 1 cc

Pituitary Solution 10 cc and 30 cc vials

**WILLIAM R. WEAVER & CO., INC.**

Ampuls Posterior Pituitary 1 cc 5 mg

**THE WARREN TEED PRODUCTS CO.**

Posterior Pituitary Injection 10 cc rubber capped vials

**THE WILSON LABORATORIES**

Ampoules Solution Posterior Pituitary Contains chlorobutanol 0.5 per cent as a preservative



## Placenta

### Gonadotropic Substances

Three types of biological substance which stimulate the gonads of either sex are to be distinguished. The fundamental physiological gonadotropic hormone of the normal animal body is produced by the anterior pituitary. The chemical nature of this material is unknown, and there is still debate as to whether there are one, two, or more pituitary gonadotropic hormones.

The serum of the pregnant mare contains a gonadotropic substance, which acts in a manner very similar to the preparations made from the anterior lobe. This substance is susceptible of refinement to a point where very little inert protein accompanies the active gonadotropic substance. It is probable that only one active compound is involved. An international unit of this substance has been defined by the special committee of the League of Nations, by comparison with a dry powder preparation supposed to be of stable potency. No preparation of this material is accepted by the Council.

The blood serum of pregnant women contains a gonadotropic substance which is distinct from that in the serum of the pregnant mare in several respects. The latter substance does not pass out into the mare's urine in appreciable amounts, whereas the urine of pregnant women contains abundant amounts of the hormone, which is termed *chorionic gonadotropic substance*.

In rodents injection of pregnancy urine, or certain extracts thereof, induces follicular growth and corpus luteum formation. When the gonadotropic activity of pregnancy urine was first demonstrated by Zondek, it was considered that the responsible substance was secreted by the anterior pituitary. At the time, the concept was advanced that this gonadotropin consisted of two hormones—prolan A, the follicle stimulating hormone, and prolan B, the luteinizing hormone—on the basis of its effect in the rat, mouse and rabbit. Further experimentation, however, has revealed that this substance is a single entity and not composed of two factors, that it arises from the placenta rather than from the pituitary, and that it differs fundamentally from the gonadotropins of the anterior lobe.

A significant physiological difference between chorionic gonadotropin and preparations from the anterior pituitary is the appreciable extent the injection of chorionic gonadotropin into primates will not induce follicular growth or corpus luteum formation. On the contrary, reliable investigators have observed definite degenerative changes in the ovaries of women and monkeys treated with this substance. In addition, it has been observed in primates that there is a marked inability of the ovaries to form follicles and corpus luteum structures.

The physiological action of chorionic gonadotropin is not limited to the female, but it exerts a definite effect on the male reproductive organs. It is generally agreed that this substance acts on the interstitial cells of the testes causing them to elaborate the androgenic hormone of the testis which in turn induces growth of the accessory sex organs. This substance is effective in male monkeys and human beings. Among the reactions induced in the monkey is the descent of the testes in the pre-puberal animal. In some animals there may be some increase

in normal immature rats

The therapeutic application of chorionic gonadotropin has covered a wide range of conditions. Many of the trials have been on an unsound or improperly conceived basis. Its use in  
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**CHORIONIC GONADOTROPIN** — *Collutein* — *Koro-trin*—The water soluble gonadotropic substance obtained from the urine of pregnant women. It is a glycoprotein containing

*Actions and Uses*—Its use is recommended in the treatment of cryptorchidism where there are no anatomic lesions causing obstruction of the testicular descent. The diagnosis of an anatomic lesion can often be made in this manner where this therapy fails. Thus the surgical treatment of cryptorchidism may be instituted at an early age when it is found that hormone monotherapy cannot induce descent. Injections should not be prolonged after six to eight weeks if no descent is obtained since excessive therapy may result in undesirable responses of precocious puberty and possibly other harmful reactions.

The diagnosis of cryptorchidism should not include those cases which have been termed pseudocryptorchids, in which the testes are maintained in the inguinal canal as the result of reflex muscular spasm. It will be found that the testes return to the normal scrotal position on gentle handling and warmth.

Chorionic gonadotropin therapy in other disorders is still considered experimental because of the lack of convincing data. The treatment of hypogonadism in the adult is considered experimental at the present time. Its value in the treatment of uterine bleeding of functional nature is also as yet unproved although numerous reports on this therapy have appeared in scientific publications. There is less enthusiasm for

this therapy at the present time than there was several years ago. Considerable disagreement exists among the various investigators regarding the type of bleeding benefited by chorionic gonadotropin therapy.

**Dosage.**—The usual dose in treating cryptorchidism is from 200 to 500 international units two to three times a week. Long-continued injections may be dangerous and treatment should not be maintained after eight weeks in the absence of progressive descent. Therapy should be discontinued on the development of signs of precocious maturity.

#### **Preparation—**

Chorionic gonadotropin is prepared from the urine of normal pregnant women by precipitating the active principle from the urine by addition of ethyl alcohol to give a concentration of more than 85 per cent alcohol, extracting the hormone from the precipitate with dilute alkaline water, and then salting out the active principle from this solution with ammonium sulfate. Further purification is made by fractionating in 50 per cent alcohol to separate most of impurities which are removed by filtration. The alcohol is removed by distillation and the residue is dried in a vacuum oven. The powder is then sealed in glass ampuls. The powder is stable for at least 1 year and is not affected by light. The powder is not toxic to rats and mice. The powder is not affected by heat up to 100°C. The powder is not affected by acids and alkalis. The powder is not affected by oxidizing and reducing agents. The powder is not affected by heavy metals. The powder is not affected by enzymes. The powder is not affected by bacteria. The powder is not affected by fungi. The powder is not affected by viruses. The powder is not affected by parasites. The powder is not affected by insects. The powder is not affected by animals. The powder is not affected by plants. The powder is not affected by minerals. The powder is not affected by vitamins. The powder is not affected by hormones. The powder is not affected by antibodies. The powder is not affected by antigens. The powder is not affected by toxins. The powder is not affected by antitoxins. The powder is not affected by vaccines. The powder is not affected by sera. The powder is not affected by cultures. The powder is not affected by tissues. The powder is not affected by organs. The powder is not affected by systems. The powder is not affected by functions. The powder is not affected by properties. The powder is not affected by characteristics. The powder is not affected by qualities. The powder is not affected by quantities. The powder is not affected by degrees. The powder is not affected by amounts. The powder is not affected by sizes. The powder is not affected by shapes. The powder is not affected by colors. The powder is not affected by odors. The powder is not affected by tastes. The powder is not affected by textures. The powder is not affected by sounds. The powder is not affected by smells. The powder is not affected by flavors. The powder is not affected by colors. The powder is not affected by odors. The powder is not affected by tastes. The powder is not affected by textures. The powder is not affected by sounds. The powder is not affected by smells. The powder is not affected by flavors. The powder is not affected by colors. The powder is not affected by odors. The powder is not affected by tastes. The powder is not affected by textures. The powder is not affected by sounds. The powder is not affected by smells. The powder is not affected by flavors.

### **E. R. Squinn & Sons**

#### **Follutein (Powder).**

**Vials Follutein, 1,000 International Units:** A powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.5 per cent of phenol, provides a solution having a potency of 100 international units per cubic centimeter.

**Vials Follutein, 5,000 International Units:** A powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.5 per cent of phenol, provides a solution having a potency of 500 international units per cubic centimeter.

**Vials Follutein, 10,000 International Units:** A powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.5 per cent of phenol, provides a solution having a potency of 1,000 international units per cubic centimeter.

Manufactured by license under U. S. patent 1,910,298

### **WINTHROP CHEMICAL COMPANY, INC.**

**Ampuls Korotrin 100 International Units:** 2 cc. A powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with the accompanying 2 cc. of sterile distilled water containing 0.2 per cent of metacresol,

provides a solution having a potency of 50 international units per cubic centimeter. Marketed in boxes of 5 ampuls with 5 ampuls korotrin diluent and in boxes of 25 ampuls without diluent.

**Ampuls Korotrin 500 International Units 2 cc.** A powdered preparation of chorionic gonadotropin admixed with sucrose which when diluted with the accompanying 2 cc of sterile distilled water containing 0.2 per cent of metacresol provides a solution having a potency of 250 international units per cubic centimeter. Marketed in boxes of 5 ampuls with 5 ampuls korotrin diluent and in boxes of 25 ampuls without diluent.

**Vials Korotrin 1 000 International Units 10 cc.** A powdered preparation of chorionic gonadotropin admixed with sucrose which when diluted with the accompanying 10 cc of sterile distilled water containing 0.2 per cent of metacresol provides a solution having a potency of 100 international units per cubic centimeter. Marketed in packages containing 1 or 10 vials with 1 or 10 bottles korotrin diluent.

**Vials Korotrin 5 000 International Units 10 cc.** A powdered preparation of chorionic gonadotropin admixed with sucrose which when diluted with suitable amounts of the accompanying 50 cc of sterile distilled water containing 0.2 per cent of metacresol provides solutions having a potency of 100 or 500 international units per cubic centimeter. Marketed in packages containing 1 vial with 1 bottle of korotrin diluent.

### Testes

Testosterone or testicular hormone has been isolated from testicular tissue and is said to be secreted by the interstitial cells. It is responsible for the development and maintenance of the accessory male organs and characteristics. Following castration in the male seminal vesicles, prostate and penis undergo severe

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efficiency of testosterone being increased through delaying absorption from the site of injection by combination with propionic acid. Testosterone is effective by percutaneous administration. Methyl testosterone, a synthetic derivative, is much more active than testosterone when given orally. The physiological action is similar. Testosterone is not excreted in the urine and should not be confused with the urinary androgens—androsterone and dehydroandrosterone—which have relatively little action on mammalian sexual tissue. Commercially testosterone is prepared synthetically and is generally marketed in

the form of testosterone propionate. This substance has shown promise in the replacement therapy of eunuchoidism, but many other claims made by promoters are unwarranted or are still in the experimental stage. The beneficial effects in treating castrates or eunuchoids are present only as long as injections are continued. The cost of such treatment in the appropriate doses is often prohibitory. It has little effect in psychic impotence or as an aphrodisiac. The relief of symptoms due to prostatism has been claimed following treatment with this substance but substantial evidence in this regard is lacking. Recent reports indicate that in adequate doses this androgen is effective in treating certain ovarian dysfunctions such as menorrhagia and dysmenorrhea. Therapy in these instances is still experimental and there has been reported the induction of significant degrees of virilism in women when the amounts of androgen administered were considerable (350-400 mg. per month). Neither testosterone nor any preparation of it stands accepted by the Council.

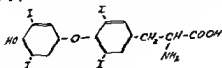
### Thyroid

**THYROID.**—"The cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man.

Thyroid contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination, and must be free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. A desiccated thyroid of a higher iodine content may be brought to this standard by admixture with a desiccated thyroid of a lower iodine content or with lactose or sodium chloride." U. S. P.

For description and standards see the U. S. Pharmacopeia under Thyroideum.

**THYROXIN.**—"An active physiological principle obtained from the thyroid gland, or prepared synthetically, and contains, when dried over sulfuric acid for 18 hours, not less than 64 per cent of iodine as an integral part of the Thyroxin molecule." U. S. P.



For description and standards see the U. S. Pharmacopeia under Thyroxinum.

**Actions and Uses.**—Thyroxin (Thyroxinum, U. S. P.) is used essentially for the same purpose as Thyroid-U. S. P., but it is claimed that with thyroxin the dosage may be more accurately determined and results more quickly obtained. Thyroxin or

Thyroid U S P are indicated in cases of diminished or absent thyroid functioning, such as cretinism and myxedema. Reports show that either preparation affects the pulse rate, blood pressure, nitrogen metabolism, relieves symptoms of myxedema and will produce hyperthyroidism. The most important quantitative measure is the determination of the basal metabolic rate. One milligram (0.001 Gm) of thyroxin

disappear. There may be loss of weight and nervous manifestations. If the dosage is continued for five or six days, the typical so called hyperthyroid symptoms may be produced: loss of weight, increased pulse rate with tachycardia, nervous manifestations and a sense of fatigue. With small doses the harmful effects are not produced and a stimulating effect is manifest in cases of myxedema. The amount of thyroxin required to produce toxic effects is exceedingly small. The maximum effect from a single injection is not reached until the second day, the duration of the effects being several weeks. In clinical medicine there is almost no use made of Thyroxin since Thyroid U S P is simpler to use, less expensive, and does not require special solution in alkali before administration.

In some forms of goiter (such as simple adolescent colloid goiter), the function of the thyroid is defective and the administration of thyroid or thyroxin may be indicated, but in many cases of goiter (especially exophthalmic) they should never be administered.

Thyroxin and thyroid have been used in obesity but increasing knowledge of this condition indicates that its treatment by restriction and management of the diet is preferable to any drug therapy.

*Dosage.*—From 0.2 mg. to 2 mg. Thyroxin should always be given at first in minimum doses and in each case the optimum amount determined by trial. For the exact determi-

0.4 mg. every day or every other day.

Thyroxin is intended for intravenous administration and is relatively ineffective by mouth. Place a known amount of pure crystalline thyroxin—from 1 to 10 mg.—in a small sterile test tube, such as is used for the Wassermann test. Add 1 drop of 10 per cent sodium hydroxide solution and about 1 cc. of water. Warm and agitate the solution until the crystals are dissolved, and then sterilize by placing the tube in boiling water. Transfer

the solution to a sterile hypodermic syringe, rinse out the test tube with 1 cc. of sterile distilled water, adding this to the solution in the syringe, and then inject the contents of the syringe intravenously.

In many cases, after symptoms of hypothyroidism have disappeared, remarkably small doses suffice to keep the patient in an almost normal state. The patient should be careful of exertion and should take sufficient protein in the diet to compensate for increased loss of nitrogen from the action of the drug.

#### HOFFMANN-LAROCHE, INC.

**Ampul Solution Synthetic Thyroxin:** 1 cc. Each one cubic centimeter contains 1 mg. of synthetic thyroxin

**Solution Synthetic Thyroxin:** Each one cubic centimeter contains 2 mg. of synthetic thyroxin

**Tablets Synthetic Thyroxin:** 1 mg.

#### E. R. SQUIBB & SONS

##### Thyroxin (Crystals).

**Thyroxin Crystals (For Intravenous Use):** 10 mg. tubes

**THYROXIN FRACTION.**—The partially purified disodium salt of thyroxin, approximately 25 per cent admixed with the acid-insoluble humus-like products of protein hydrolysis

**Actions and Uses.**—The same as those of thyroxin, except that it is not to be used for injection. In certain individuals in whom the thyroxin equivalent is not absorbed quantitatively, the pure crystalline thyroxin should be given intravenously (see under Thyroxin).

**Dosage.**—Thyroxin fraction is supplied in the form of tablets for oral administration, representing a stated weight of thyroxin. Thyroxin fraction must not be administered intravenously.

##### Tests and Standards.—

Thyroid glands of an animal are extracted with sodium hydroxide solution, the insoluble materials are removed, the filtrate is treated with hydrochloric acid and filtered, the residue is washed with water, the filtrate and washings are combined, the residue is dried and redissolved in water. The thyroxin content is determined by the assay described below and the product made into tablets with sucrose and lactose as vehicles.

Thyroxin fraction is a light brown powder having a characteristic odor and an alkaline taste. It is soluble in water; decomposed by acids. The following method may be applied for the assay of the tablets.

Weigh accurately five or ten tablets. Grind finely the tablets and weigh out a sample of the powdered material for analysis, place over sulfuric acid in a desiccator for twenty-four hours and determine loss in weight. Deliver the dried sample in a beaker and add 10 cc. sodium hydroxide solution, 30 per cent. Dissolve the sample by "working" it with the aid of a glass rod; add 50 cc. of water. Filter the solution into a small beaker, wash the original beaker and filter paper with sodium hydroxide test solution. Make the filtrate faintly acid with dilute sulfuric acid solution, filter off the precipitate and

## L. R. SQUIBB &amp; SONS

**Tablets Thyroxin Fraction** Equivalent to 0.2 mg, 0.4 mg, 0.8 mg and 2.0 mg of thyroxin

Manufactured by license of the University of Minnesota U. S. patents 1,392,767 and 1,392,768 (Oct. 4, 1921 exp. red.)



## CHAPTER XVII

### METABOLIC AGENTS

#### Calcium Compounds

Calcium performs important functions, especially in forming the structure of bone, in the regulation of nervous and muscular activity, and in the coagulation of the blood. In rickets, osteomalacia and osteopsathyrosis there is defective deposition of calcium in the bones, but this is usually due to factors other than a deficient supply of calcium; and these conditions are not benefited by the administration of calcium salts except in rare experimental conditions, when calcium has been almost totally lacking in the diet. When the calcium content of the blood is low, as in infantile and parathyroid tetany, the administration of calcium salts results in a temporary increase in blood calcium and a cessation of the symptoms, but unless the cause of the condition is removed, the concentration sinks rapidly following discontinuance of calcium administration. Administration of the parathyroid hormone leads to an increase in blood calcium even though additional calcium is not supplied.

The administration of calcium salts has been shown to lessen

There is some clinical evidence,

use of calcium salts for vari-

oneurotic edema. Intravenous

ounds has been shown

d therefore is useful in

pain (Aub and Bauer,

ysiol. 97:1421, 1931)

Calcium chloride has been shown to be useful in treating edema in certain types of Bright's disease and the ascites of cirrhosis of the liver. It is unreliable against ascites and other generalized edemas. It has been reported as being effective in preventing arsphenamine reactions and also in certain dermatoses, as dermatitis herpetiformis, lichen rubra and erythema pernio, but further observations are needed in these directions. A deficiency of calcium in the circulating fluids leads to increased excitability of the neuromuscular system, as is seen for example in tetany. The administration of calcium salts decreases the neuromuscular irritability in such cases. The intravenous infusion of soluble calcium salts causes a constriction of the blood vessels and a marked contraction of the pupils.

Calcium is necessary for blood coagulation, but a large excess lengthens the coagulation time. The effect of calcium on blood coagulation has led to its inj conditions, such as hemophilia, rhage of typhoid fever. It is in any of these conditions, as an adequate amount of calcium. It has been shown that administration of calcium salts tends to diminish the toxicity of

carbon tetrachloride. When calcium chloride is administered the basic portion of the molecule is, to a large extent, excreted by way of the bowel. The acid portion behaves in the same manner as hydrochloric acid from other sources, decreasing the alkali reserve of the body and increasing the acidity of the urine. Large doses of calcium chloride may produce acidosis. Calcium chloride is one of the substances which may be administered to render the urine acid.

Intravenously, overdoses of calcium compounds may be fatal by paralyzing the heart and central nervous system.

It has been reported that not infrequently the American diet contains basal or sufficient amount of calcium to meet the needs.

tration of calcium salts in the treatment of rickets or other diseases associated with deficient calcification is in itself inefficient, but may be used as an adjunct in the treatment when

tration. The absorption of calcium chloride from the intestines probably plays no greater part than that which would result from the administration of any other calcium salt. The lactate and gluconate are, however, more pleasant to take than calcium chloride and are less irritating. Calcium chloride cannot be used for subcutaneous or intramuscular injection as it is too irritating. It may, however, be used intravenously. For hypodermic or intramuscular use the less irritant lactate or the non irritant gluconate are employed.

**AFENIL** — Calcium chloride urea —  $\text{CaCl}_2 \cdot 4(\text{NH}_2)_2\text{CO}$  — Afenil is a molecular compound of calcium chloride and urea.

**Actions and Uses** — Afenil has the actions of calcium chloride. It is claimed that afenil solutions when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

**Dosage** — Afenil is marketed in ampuls containing 10 cc. of a 10 per cent solution of afenil. Each injection consists of the entire contents of one ampul.

#### *Tests and Standards* —

Afenil occurs as colorless crystals, non hygroscopic, very soluble in water.

The calcium content of afenil is determined by precipitating with ammonium oxalate in the usual way and weighing as calcium oxide. The urea content of afenil is determined by an estimation of nitrogen by the Kjeldahl method.

## BILHUIER-KNOLL CORP.

**Ampules Solution Afenil:** 10 cc. of a sterile 10 per cent solution (equivalent to 0.11 Gm Ca).

U. S. trademark 170,032. German patent 306,801.

**CALCIUM GLUCONATE.**—"Contains not less than 88 per cent and not more than 93 per cent of calcium (Ca), corresponding to not less than 99 per cent of  $\text{Ca}(\text{C}_6\text{H}_{11}\text{O}_7)_2 \cdot \text{H}_2\text{O}$ " U. S. P.

For description and standards see the U. S. Pharmacopeia under *Calcii Gluconas* and *Injectio Calcii Gluconatis*.

**Actions and Uses.**—Calcium gluconate is used to obtain the therapeutic effects of calcium. It is more palatable than calcium chloride for oral administration, and is nonirritant for hypodermic or intramuscular use.

**Dosage.**—Orally, for adults, 5 Gm. three times a day; for children, 2 Gm. three times a day. Intramuscularly or intravenously, for adults, 1 Gm. administered every day, on alternate days or every third day; for children, 0.2 to 0.5 Gm. administered every day, on alternate days or every third day.

**Calcium d-Saccharate:** The calcium d-saccharate used as a stabilizing agent in these solutions of calcium gluconate so stabilized complies with the following tests and standards:

Calcium d-saccharate occurs as a fine, white, odorless tasteless powder, which is stable in air. It is slightly soluble in water, ether, alcohol and chloroform. A saturated solution of calcium d-saccharate is neutral to litmus and possesses a pH of about 6.0.

Transfer about 0.1 Gm. of calcium d-saccharate to a test tube, add 10 cc. of water and 1 cc. of diluted hydrochloric acid; the resultant solution is clear and colorless. To this solution add 5 cc. of ammonium oxalate solution; a white precipitate appears, which is soluble in diluted hydrochloric acid.

Dissolve 0.5 Gm. of calcium d-saccharate in 10 cc. of water and 2 cc. of diluted hydrochloric acid, and boil the solution for two minutes. Cool, add 5 cc. of sodium carbonate solution, allow to stand for five minutes, dilute to 20 cc. with distilled water and filter. Add 5 cc. of the filtrate to 2 cc. of alkaline cupric tartrate solution and boil for one minute; no red precipitate is formed (*dextrose and sucrose*).

One Gm. of calcium d-saccharate shows no more chloride when tested with diluted nitric acid and silver nitrate solution than 1 cc. of fifth normal hydrochloric acid. A 2 Gm. portion of calcium d-saccharate shows no more sulfate than corresponds to 1 cc. of fifth normal sulfuric acid when tested with diluted hydrochloric acid and barium chloride solution. Dissolve 1 Gm. of calcium d-saccharate in 10 cc. of distilled water and 3 cc. of diluted hydrochloric acid; add 10 cc. of hydrogen sulfide solution; no precipitate appears, and the color is not darker than a faint brown (*heavy metals*).

Transfer approximately 0.4 Gm. of calcium d-saccharate, dried over sulfuric acid and accurately weighed, to a 250 cc. beaker, and dissolve in 100 cc. of distilled water and 2 cc. of hydrochloric acid. Add an excess of ammonium oxalate solution, heat to boiling, and slowly neutralize with ammonia water, with stirring. Digest the mixture on a water bath for one hour, filter on hardened filter paper and wash thoroughly with warm distilled water. Puncture the filter paper, wash

the precipitate into a beaker by means of a stream of hot distilled water followed by 30 cc of diluted (1:3) sulfuric acid. Heat the solution to 60 C and titrate with tenth normal potassium permanganate. The calcium oxide content is not less than 17.3 and not more than 17.7 per cent.

#### ARBOTT LABORATORIES

Calcium Gluconate (*Powder*) bulk

Ampule Solution Calcium Gluconate 10%, 10 cc

Tablets Calcium Gluconate (Flavored) 1 Gm

#### GEORGE A. BREON & COMPANY, INC.

Ampul Solution Calcium Gluconate 10%, W/V 10 cc

Each ampul contains a sterile aqueous solution of calcium gluconate U. S. P. 10 Gm stabilized with calcium D-saccharate 0.02 Gm.

#### ENDO PRODUCTS, INC.

Ampul Solution Calcium Gluconate 10%, W/V Stabilized with Calcium D-Saccharate 0.8%, W/V 10 cc

Each ampul contains a sterile aqueous solution of calcium gluconate U. S. P. 10 Gm stabilized with calcium D-saccharate 0.08 Gm.

#### THE LAKESIDE LABORATORIES, INC.

Ampul Solution of Calcium Gluconate 10%, W/V

Stabilized with Calcium D-Saccharate 0.5%, W/V 10 cc  
Each ampul contains a sterile aqueous solution of calcium gluconate U. S. P. 10 Gm stabilized with calcium D-saccharate 0.05 Gm.

#### MATTHEI CHEMICAL CO.

Ampul Calcium Gluconate 10%, W/V 10 cc

#### MERCK & CO., INC.

Calcium Gluconate (*Powder*) bulk

#### PARKER DAVIS & COMPANY

Compressed Tablets Calcium Gluconate 0.5 Gm and 1 Gm

#### CHAS. PFIZER & CO., INC.

Calcium Gluconate (*Powder*) bulk

U. S. trademark 142,090

#### SANDOZ CHEMICAL WORKS, INC.

Calcium Gluconate (*Powder*) bulk

Ampules Solution Calcium Gluconate 10%, 10 cc

U. S. patent 1,645,363 (Nov. 8, 1927 exp. res. 1944)

## THE UPJOHN COMPANY

**Ampoules Calcium Gluconate Solution 10% W/V**  
 Stabilized with Calcium *d*-Saccharate 0.35% W/V: 10 cc  
 Each ampul contains a sterile aqueous solution of calcium gluconate-U. S. P., 1.0 Gm. stabilized with calcium *d*-saccharate 0.035 Gm.

**Wafers Calcium Gluconate (Flavored):** 0.96 Gm. Each wafer contains calcium gluconate-U. S. P., 15 Gm with sugar talc, dye and oil of wintergreen for flavoring.

## U. S. STANDARD PRODUCTS CO.

**Ampules Compound Solution of Calcium Gluconate, 10%:** 10 cc. A solution containing in each 10 cc. calcium gluconate, 1 Gm.; dextrose anhydrous, 0.5 Gm; citric acid, 0.037 Gm., and lactic acid, 0.1 Gm.

**CALCIUM GLUCONATE EFFERVESCENT:** A granular mixture containing calcium gluconate, 50%; citric acid, 25%, and sodium bicarbonate, 25%.

*Actions and Uses*—See calcium gluconate.

*Dosage*—Orally for adults, 10 Gm three times a day; for children, 4 Gm. three times a day

*Tests and Standards.*—

Calcium gluconate effervescent occurs as a white, coarsely granular odorless material, with a biting acid taste. Its solubility in water is not less than 28 Gm. per hundred cubic centimeters at 25 C.; the resulting solution is acid to litmus. The loss in weight over sulfuric acid is not greater than 0.5 per cent. The product conforms to tests for purity of calcium gluconate-U. S. P.; the calcium oxide content is not less than 6.0 per cent nor more than 6.4 per cent.

Dissolve approximately 5 Gm. of calcium gluconate effervescent, accurately weighed, in water to make 100 cc. of solution; transfer a 25 cc. portion to a 250 cc. beaker, boil for two minutes and, while boiling, add 25 cc. of a hot saturated solution of calcium hydroxide and continue boiling for five minutes, digest on the steam bath for two hours and filter while hot through a hot Gooch crucible, wash the residue with boiling water and dry to constant weight at 100 C.; the citric acid content is not less than 24.5 per cent nor more than 25.8 per cent. Dissolve approximately 10 Gm. of calcium gluconate, effervescent, accurately weighed, in water to make 100 cc. of solution; transfer a 25 cc. portion to a suitable Erlenmeyer flask, boil for two minutes, cool, and titrate with tenth normal sodium hydroxide using phenolphthalein as an indicator; a 1 Gm. sample requires not less than 7 cc., nor more than 7.6 cc. of tenth normal sodium hydroxide. Transfer about 0.1 Gm. of calcium gluconate effervescent, accurately weighed, to a 150 cc. beaker and dissolve in 5 cc. of distilled water; cool the beaker and contents in ice water and add 25 cc. of a 15 per cent magnesium uranyl acetate solution; place the mixture in an ice bath at 20 C. and allow to stand for twenty-four hours; filter with suction and wash with 95 per cent alcohol saturated with sodium magnesium uranyl acetate, dry the precipitate at 110 C. for thirty minutes, cool and weigh. One Gm. of sodium magnesium uranyl acetate being equivalent to 0.0153 Gm. of sodium, the sodium content is not less than 6.4 per cent nor more than 7.0 per cent.

## FLINT, EATON &amp; COMPANY

Calcium Gluconate Effervescent (Powder); bulk

U S patent 1 983 954

**CALCIUM LEVULINATE.**—The dihydrated normal calcium salt of levulinic acid— $(CH_3COCH_2CH_2COO)_2Ca \cdot 2H_2O$ —M W. 306.32

**Actions and Uses.**—Calcium levulinate is used to obtain the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

**Dosage.**—By injection, for adults, 1 Gm daily or on alternate days, for children, 0.2 to 0.5 Gm. Orally, for adults, 4 to 5 Gm three times a day; for children, 1 to 2 Gm three times a day.

**Tests and Standards.**—

Calcium levulinate occurs as an odorless or nearly odorless white, crystalline or a freely soluble powder. It is soluble in acetone and slightly decomposed during the assay. It is a calcium salt of levulinic acid.

Dissolve 1 Gm of calcium levulinate in 10 cc of water, a clear, colorless solution is formed. A 5 cc. portion of this solution responds to the U S P tests for calcium. To the other 5 cc portion add 5 cc of sodium hydroxide solution, filter and add to the filtrate 5 cc of iodine test solution; the iodine color disappears and a pale yellow precipitate of iodoform appears.

Dissolve 0.1 Gm. of calcium levulinate in 2 cc of water and add

of reducing sugars)

Four Gm of calcium levulinate show no more chloride than corresponds to 1 cc of fifth normal hydrochloric acid (U S P XII, p. 626). Eight Gm of calcium levulinate show no more sulfate than corresponds to 1 cc of fifth normal sulfuric acid (U S P XII, p. 626). Dissolve 1 Gm. of calcium levulinate in 10 cc of 5 per cent

tained in a tared weighing dish of 40 to 50 mm diameter, in a hot air oven at 105 C for 24 hours. The loss in weight is not less than 10.8 per cent nor more than 11.7 per cent.

Transfer about 3.0 Gm of calcium levulinate, accurately weighed to a 500 cc calibrated flask, using a small quantity of water, add 10 cc of hydrochloric acid and dilute to the mark with water. Transfer 100 cc of the solution to a 250 cc beaker, heat to boiling, and continue the assay for calcium as directed in the U S P XII under

**Calcii Gluconate.** Each cc. of tenth-normal potassium permanganate is equivalent to 0.0111 gm. of anhydrous calcium levulinate. The amount of calcium levulinate found corresponds to not less than 99 per cent nor more than 100.5 per cent, calculated to the dried substance.

**HUTCHINSON WATSON & Co., Inc.**

**Hypoid Calcium Levulinate Injection 10% Solution:**  
1 Gm. in 10 cc.

**PALL LABORATORIES, Inc.**

**Calcium Levulinate (Powder):** Bulk. Packed in 45.3 Gm. and 2165, 453, 10825, 2165 and 45.3 Kg. packages.

### Iodine Compounds for Systemic Use

These are typified by sodium iodide and potassium iodide. The mechanism of their action is not clearly understood. The most definite results are seen in the rapid absorption of certain inflammatory exudates and especially of the gummatous lesions of tertiary syphilis. Lesions of this type in bone, skin, brain, or other organs diminish or disappear under adequate doses of the drug. In actinomycosis and sporotrichosis the action of iodide is almost specific. The iodide ion is not germicidal.

The beneficial effect of iodides in arteriosclerosis and aneurysm is probably limited to the absorption of syphilitic deposits in the vessel wall. The iodides do not directly lower blood pressure. They may tend to affect the production of thyroxine and may thus exert an indirect effect on metabolism. Iodides in very small amounts are effective in the prophylaxis of simple endemic goiter, and in controlling the symptom of hyperthyroidism in preparation for operation.

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, such as coryza and skin eruptions. Experience confirms in a measure the former claim, but the latter is misleading. Iodism is probably a necessary manifestation of the full physiological activity of the drug. If, therefore, a preparation consistently fails to elicit these characteristic symptoms, it may be presumed that the amount of the drug absorbed is insufficient to produce the full effects, such as are required in the treatment of syphilis, although it may suffice in conditions for which a milder action is desired. Clinical observations establish the fact that the organic iodides, in the dosage ordinarily employed, are weaker than full doses of the inorganic forms.

**Harming.** The intravenous injection of sodium iodide is a dangerous proceeding. While it is tolerated in many cases without bad effects, it may produce not only acute and violent iodism, but also colloidoclastic shock and pulmonary edema. It should therefore not be employed to secure the ordinary actions of iodides, except in very special and restricted conditions, such as (1) certain rare cases of acute thyrotoxicosis with severe vomiting, and (2) in severe paroxysms of asthma.

### Sodium Iodide

**SODIUM IODIDE.**—When dried to constant weight at 120° C., contains not less than 99 per cent NaI. U. S. P.

For description and standards see the U. S. Pharmacopeia under Sodium Iodide and the National Formulary under Annullae Sodii Iodidi.

**Actions, Uses and Dosage**—See the general article (volume Compounds for Systemic Use

## ENDO PRODUCTS, INC.

Ampoules Solution Sodium Iodide, 10%, W/V. 10 cc and 20 cc. Each 10 cc contains 10 Gm of sodium iodide

**Ampoules Solution Sodium Iodide, 20%, W/V** 10 cc  
Each 10 cc contains 20 Gm of sodium iodide

## THE LAKESIDE LABORATORIES, INC.

**Ampules Solution Sodium Iodide 10%, (W/V):** 10 cc and 20 cc. Each 10 cubic centimeters contains 10 Gm of sodium iodide.

**Ampules Solution Sodium Iodide 20%, (W/V):** 10 cc [10] 10 cubic centimeters contains 20 Gm of sodium iodide

### ***Iodine-Protein Compounds***

Iodalbum and iodo casein appear to suffer little change in the acid contents of the stomach but on passing into the intestines they are dissolved and decomposed by contact with the alkaline secretion and absorbed chiefly, if not entirely, as iodide ions, their actions and uses are therefore identical with those of the inorganic iodides. The slower absorption may result in a more continuous action, but this seems to be of small importance.

**IODALBIN**—A compound of iodine and blood albumin containing approximately 215 per cent of iodine

**Actions and Uses** ~ See preceding article, Iodine Protein Compounds

**Dosage**—From 0.3 to 0.6 Gm repeated according to indications.

#### Preparation and Tests—

Iodalbin is prepared by treating blood albumin with a solution of iodine whereby an insoluble precipitate is produced. This precipitate is separated, purified by the removal of free iodine, dried, powdered and assayed.

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log = " "
mc = " "
orc = " "
mc = " "

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## CHAPTER XVIII

### PARENTERAL SOLUTIONS

#### Dextrose

**DEXTROSE.**—*d*-Glucose.— $\text{CH}_2\text{OH}.\text{CH}(\text{CHOH})_4.\text{CHOH}.$   
 $\text{H}_2\text{O}$ . "A sugar usually obtained by the hydrolysis of starch."  
*U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under *Dextrosum*, *Injectio Dextrosi* and *Injectio Dextrosi et Sodii Chloridi*.

Dextrose is a readily absorbable food. Its solutions, which are being extensively used in modern therapy, may be administered for parenteral alimentation by hypodermic or intravenous injection. Alone or in combination with various salt solutions, they are used to supply fluid, to sustain the blood volume temporarily, or to produce diuresis. Primarily they are intended to supply dextrose to the patient without disturbing the gastrointestinal tract. The strength of the solution, the medium (distilled water, isotonic solution of sodium chloride, or Ringer's solution), as well as the total quantity and route of administration must be varied to meet the indications of the individual case.

Subcutaneous injections are necessarily low in dextrose content (2.5 per cent in isotonic solution of sodium chloride); intravenous solutions may vary in strength from 5 to 50 per cent of dextrose. Slow rate of flow is essential to the proper administration of these solutions and is especially important in cases of hemorrhage which are not entirely controlled. If it is necessary to supply very large amounts of dextrose to the individual in a relatively short time, small amounts of high concentration are generally preferable to greater amounts of lower concentration.

These solutions are often warmed so that they may enter the vein at body temperature. The entire apparatus (bottle or flask, rubber tubing, connections, and needle) must be sterile and the entire line of rubber tubing, as well as the needle, must be freed of air bubbles before the needle is inserted. The area in which the needle is injected must also be adequately prepared. The intake air should be filtered by a cotton pledget or other adequate device.

The administration of these solutions should be instituted by a physician and continued under his supervision (especially intravenous injection), and must be discontinued before the container is empty. Intraperitoneal injections are not recommended because they cause distention which may be prolonged and may induce a sterile peritonitis with polymorphonuclear exudation.

Frequently apparatus used for the administration of intravenous solutions is used repeatedly. Before the apparatus is again used it must be sterilized, this sterilization process to be

preceded by rinsing several times in distilled water. This should eliminate any untoward reactions which may be due to the lack of such thorough cleansing.

Since the official dextrose of the U. S. P. XI contains one molecule of water of crystallization, physicians should bear in mind that a solution labeled in terms of dextrose U. S. P. will actually contain a less amount of anhydrous dextrose. However, in prescribing there should be reference to hydrous dextrose in conformity with U. S. P. practice. The physician should bear in mind that in more concentrated solutions of dextrose there is considerable variation in content when comparing dex

of dextrose U. S. P.

Dextrose 33 $\frac{1}{3}$  per cent has been recommended by the originators of insulin therapy of schizophrenia in the management of the shock which may follow the administration of insulin.

*Dosage*—The dosage of dextrose in a single injection varies with the strength of the solution and may range between 5 and 250 Gm. with the different purposes for which the solutions are used.

#### ABBOTT LABORATORIES

**Ampoules Solution Dextrose 50%, W/V** 10 cc 20 cc 50 cc and 100 cc. Each 10 cc of solution contains 5 Gm. of dextrose in distilled water.

**Dextrose 5%, W/V in Distilled Water** 250 cc 500 cc 1 000 cc and 2 000 cc bottles. Each 100 cc contains 5 Gm. of dextrose.

**Dextrose 10%, W/V in Distilled Water** 250 cc 500 cc 1 000 cc and 2 000 cc bottles. Each 100 cc contains 10 Gm. of dextrose.

**Dextrose 20%, W/V in Distilled Water** 500 cc and 1 000 cc bottles. Each 100 cc contains 20 Gm. of dextrose.

**Dextrose 2 $\frac{1}{2}$ %, W/V in Isotonic Sodium Chloride Solution** 500 cc 1 000 cc and 2 000 cc bottles. Each 100 cc contains 2.5 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 5%, W/V in Isotonic Sodium Chloride Solution** 250 cc 500 cc 1 000 cc and 2 000 cc bottles. Each 100 cc contains 5 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 10%, W/V in Isotonic Sodium Chloride Solution** 250 cc 500 cc 1 000 cc and 2 000 cc bottles. Each 100 cc contains 10 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 25% W/V in Isotonic Sodium Chloride Solution:** 500 cc. and 1,000 cc. bottles. Each 100 cc. contains 25 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 5% W/V in Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. bottles. Each 100 cc. contains 5 Gm. of dextrose, 0.86 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.033 Gm. of calcium chloride.

**Dextrose 10% W/V in Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. bottles. Each 100 cc. contains 10 Gm. of dextrose, 0.86 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.033 Gm. of calcium chloride.

**Dextrose 5% W/V in Lactate-Ringer's Solution:** 500 cc. and 1,000 cc. bottles. Each 100 cc. contains 5 Gm. of dextrose, 0.31 Gm. of sodium lactate, 0.6 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.02 Gm. of calcium chloride.

**Dextrose 10% W/V in Lactate-Ringer's Solution:** 500 cc. and 1,000 cc. bottles. Each hundred cubic centimeters contains dextrose 10 Gm., sodium lactate 0.31 Gm., sodium chloride 0.6 Gm., potassium chloride 0.03 Gm. and calcium chloride 0.02 Gm.

#### **BAXTER LABORATORIES, INC.**

**Sterile Dextrose Solution 5% W/V:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 5 Gm. of dextrose in distilled water.

**Sterile Dextrose Solution 7½% W/V:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 7.5 Gm. of dextrose in distilled water.

**Sterile Dextrose Solution 10% W/V:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 10 Gm. of dextrose in distilled water.

**Sterile Dextrose Solution 20% W/V:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 20 Gm. of dextrose in distilled water.

**Sterile Dextrose Solution 25% W/V:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 25 Gm. of dextrose in distilled water.

**Sterile Dextrose 2½% W/V in Isotonic Solution of Sodium Chloride:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 2.5 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 5% W/V in Isotonic Solution of Sodium Chloride:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 5 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 7½%, W/V in Isotonic Solution of Sodium Chloride** 500 cc, 1000 cc and 2000 cc Vacoliter containers Each 100 cc contains 7.5 Gm of dextrose and 0.90 Gm of sodium chloride

**Sterile Dextrose 10%, W/V in Isotonic Solution of Sodium Chloride** 500 cc 1000 cc and 2000 cc Vacoliter containers Each 100 cc contains 10 Gm of dextrose and 0.90 Gm. of sodium chloride

**Sterile Dextrose 20%, W/V in Isotonic Solution of Sodium Chloride** 500 cc, 1000 cc and 2000 cc Vacoliter containers Each 100 cc contains 20 Gm of dextrose and 0.90 Gm of sodium chloride

**Sterile Dextrose 25%, W/V in Isotonic Solution of Sodium Chloride** 500 cc 1000 cc and 2000 cc Vacoliter containers Each 100 cc, contains 25 Gm of dextrose and 0.90 Gm of sodium chloride

**Dextrose 5%, W/V in Isotonic Solution of Three Chlorides** 500 cc and 1000 cc Vacoliter containers Each 100 cc contains 5 Gm of dextrose 0.86 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.033 Gm of calcium chloride

**Dextrose 10%, W/V in Isotonic Solution of Three Chlorides** 500 cc and 1000 cc Vacoliter containers Each 100 cc contains 10 Gm of dextrose 0.86 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.033 Gm of calcium chloride

**Dextrose 5%, W/V in Lactate Ringer's Solution** 500 cc and 1000 cc Vacoliter containers Each 100 cc contains 5 Gm of dextrose 0.31 Gm of sodium lactate 0.6 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.02 Gm of calcium chloride

**Dextrose 10%, W/V in Lactate Ringer's Solution** 500 cc and 1000 cc Vacoliter containers Each 100 cc contains 10 Gm of dextrose 0.31 Gm of sodium lactate 0.6 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.02 Gm of calcium chloride

#### DON BAXTER INC

**Sterile Dextrose Solution 5%, W/V** 500 cc 1000 cc and 2000 cc Vacoliter containers Each 100 cc contains 5 Gm of dextrose in distilled water

**Sterile Dextrose Solution 10%, W/V** 500 cc 1000 cc and 2000 cc Vacoliter containers Each 100 cc contains 10 Gm of dextrose in distilled water

**Sterile Dextrose Solution 20%, W/V** 500 cc and 1000 cc Vacoliter containers Each 100 cc contains 20 Gm of dextrose in distilled water

**Sterile Dextrose Solution 25% W/V:** 500 cc. Vacoliter containers. Each 100 cc. contains 25 Gm. of dextrose in distilled water.

**Sterile Dextrose 2½% W/V in Isotonic Solution of Sodium Chloride:** 500 cc. and 1,000 cc. Vacoliter containers. Each 100 cc. contains 2.5 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 5% W/V in Isotonic Solution of Sodium Chloride:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 5 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 7½% W/V in Isotonic Solution of Sodium Chloride:** 1,000 cc. Vacoliter containers. Each 100 cc. contains 7.5 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 10% W/V in Isotonic Solution of Sodium Chloride:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 10 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 20% W/V in Isotonic Solution of Sodium Chloride:** 500 cc. Vacoliter containers. Each 100 cc. contains 20 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterile Dextrose 25% W/V in Isotonic Solution of Sodium Chloride:** 500 cc. Vacoliter containers. Each 100 cc. contains 25 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Dextrose 5% W/V in Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. Vacoliter containers. Each 100 cc. contains 5 Gm. of dextrose, 0.86 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.033 Gm. of calcium chloride.

**Dextrose 10% W/V in Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. Vacoliter containers. Each 100 cc. contains 10 Gm. of dextrose, 0.86 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.033 Gm. of calcium chloride.

**Dextrose 5% W/V in Lactate-Ringer's Solution:** 500 cc. and 1,000 cc. Vacoliter containers. Each hundred cubic centimeters contains dextrose 5.0 Gm., sodium lactate 0.31 Gm., sodium chloride 0.6 Gm., potassium chloride 0.03 Gm. and calcium chloride 0.02 Gm.

**Dextrose 10% W/V in Lactate-Ringer's Solution:** 500 cc. and 1,000 cc. Vacoliter containers. Each hundred cubic centimeters contains dextrose 10.0 Gm., sodium lactate 0.31 Gm., sodium chloride 0.6 Gm., potassium chloride 0.03 Gm. and calcium chloride 0.02 Gm.

**GEORGE A. BREON & COMPANY, INC.**

**Ampule Solution Dextrose 50% W/V:** 50 cc. Each 50 cc contains 25 Gm of dextrose in distilled water

**CHEPLIN BIOLOGICAL LABORATORIES, INC.**

**Ampule Solution Dextrose (50% W/V):** 20 cc. A solution of dextrose 50 per cent W/V in distilled water

**CONTINENTAL HOSPITAL LABORATORIES, INC.**

**Dextrose 5% W/V in Distilled Water:** 500 cc and 1,000 cc bottles. Each 100 cc contains 5 Gm of dextrose

**Dextrose 10% W/V in Distilled Water:** 500 cc and 1,000 cc bottles. Each 100 cc contains 10 Gm of dextrose

**Dextrose 20% W/V in Distilled Water:** 500 cc and 1,000 cc bottles. Each 100 cc contains 20 Gm of dextrose

**Dextrose 2½% W/V in Isotonic Solution of Sodium Chloride:** 500 cc and 1,000 cc bottles. Each 100 cc contains 25 Gm of dextrose and 0.9 Gm of sodium chloride-U S P

**Dextrose 5% W/V in Isotonic Solution of Sodium Chloride:** 500 cc and 1,000 cc bottles. Each 100 cc contains 5 Gm of dextrose and 0.9 Gm of sodium chloride U S P

**Dextrose 10% W/V in Isotonic Solution of Sodium Chloride:** 500 cc and 1,000 cc bottles. Each 100 cc contains 10 Gm of dextrose and 0.9 Gm of sodium chloride-U S P

**Dextrose 5% W/V in Isotonic Solution of Three Chlorides:** 500 cc and 1,000 cc bottles. Each 100 cc contains 5 Gm of dextrose, 0.86 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.033 Gm of calcium chloride

**CUTLER LABORATORIES**

**Solution Dextrose 5% W/V:** 250 cc, 500 cc, 1,000 cc and 2,000 cc. Safeflask containers. Each 100 cc contains 5 Gm of dextrose in distilled water

**Solution Dextrose 10% W/V:** 250 cc, 500 cc, 1,000 cc and 2,000 cc. Safeflask containers. Each 100 cc contains 10 Gm of dextrose in distilled water

**Solution Dextrose 20% W/V:** 500 cc and 1,000 cc. Safeflask containers. Each 100 cc contains 20 Gm of dextrose in distilled water

**Solution Dextrose 25% W/V:** 500 cc and 1,000 cc. Safeflask containers. Each 100 cc contains 25 Gm of dextrose in distilled water

**Solution Dextrose 50% W/V:** 50 cc and 100 cc bottles. Each 10 cc contains 5 Gm of dextrose in distilled water

**Solution Dextrose 2½% W/V in Isotonic Solution of Sodium Chloride:** 250 cc, 500 cc, 1,000 cc, and 2,000 cc. Safeflask containers. Each 100 cc contains 25 Gm of dextrose and 0.9 Gm of sodium chloride

**Solution Dextrose 5% W/V in Isotonic Solution of Sodium Chloride:** 250 cc., 500 cc., 1,000 cc., and 2,000 cc. Safflask containers. Each 100 cc. contains 5 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Solution Dextrose 10% W/V in Isotonic Solution of Sodium Chloride:** 250 cc., 500 cc., 1,000 cc., and 2,000 cc. Safflask containers. Each 100 cc. contains 10 Gm. of dextrose and 0.9 Gm. of sodium chloride.

#### ENDO PRODUCTS, INC.

**Ampoules Solution Dextrose 50% W/V:** 20 cc., 50 cc. and 100 cc. Each 10 cc. of solution contains 5 Gm. of dextrose in distilled water.

#### FLINT, EATON & COMPANY

**Ampul Solution Dextrose 50% (W/V):** 50 cc. and 100 cc. Each 100 cc. contains 50 Gm. of dextrose in distilled water.

#### HOSPITAL LIQUIDS, INC.

**Dextrose 5% W/V in Distilled Water:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 5 Gm. of dextrose.

**Dextrose 10% W/V in Distilled Water:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 10 Gm. of dextrose.

**Dextrose 20% (W/V) in Distilled Water:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 20 Gm. of dextrose.

**Dextrose 25% W/V in Distilled Water:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 25 Gm. of dextrose.

**Dextrose 50% (W/V) in Distilled Water:** 50 cc. and 100 cc. vials. Each 100 cc. contains 50 Gm. of dextrose.

**Dextrose 2½% (W/V) in Isotonic Sodium Chloride Solution:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 2.5 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 5% W/V in Isotonic Sodium Chloride Solution:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 5 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 7½% (W/V) in Isotonic Sodium Chloride Solution:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 7.5 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 10% W/V in Isotonic Sodium Chloride Solution:** 500 cc., 1,000 cc. and 2,000 cc. Filtrair containers. Each 100 cc. contains 10 Gm. of dextrose and 0.9 Gm. of sodium chloride.

**Dextrose 20% (W/V) in Isotonic Sodium Chloride Solution** 500 cc 1000 cc and 2000 cc Filtrair containers  
Each 100 cc contains 20 Gm of dextrose and 0.9 Gm of sodium chloride

**Dextrose 5% (W/V) in Isotonic Solution of Three Chlorides** 500 cc 1000 cc and 2000 cc Filtrair containers  
Each 100 cc contains 5 Gm of dextrose 0.7 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.025 Gm of calcium chloride

**Dextrose 10% (W/V) in Isotonic Solution of Three Chlorides** 500 cc 1000 cc and 2000 cc. Filtrair containers  
Each 100 cc contains 10 Gm of dextrose 0.7 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.025 Gm of calcium chloride

#### THE LAKESIDE LABORATORIES INC

**Ampoules Solution Dextrose (50% W/V)** 10 cc 20 cc 50 cc. and 100 cc Each 10 cc contains 5 Gm of dextrose in distilled water

**Sterile Solution Dextrose (50% W/V)** 50 cc and 100 cc vials Each 10 cc contains 5 Gm of dextrose in distilled water

#### ELI LILLY AND COMPANY

**Ampoules Solution Dextrose (50% W/V)** 50 cc and 100 cc Each 10 cc contains 5 Gm of dextrose in distilled water

#### THE WM S MERRILL COMPANY

**Ampuls Solution Dextrose 50% W/V** 20 cc., 50 cc. and 100 cc Each 10 cc contains 5 Gm of dextrose in distilled water

#### E S MILLER LABORATORIES INC

**Ampoules Sterile Solution Dextrose (50% W/V)** 10 cc 20 cc 50 cc and 100 cc. Each 10 cc contains 5 Gm of dextrose in distilled water

**Sterile Solution Dextrose (50% W/V)** 10 Gm in 20 cc., 25 Gm in 50 cc and 50 Gm in 100 cc. vials Each 10 cc contains 5 Gm. of dextrose in distilled water

#### THE NATIONAL DRUG CO

**Ampuls Solution of Dextrose 50% W/V** 20 cc and 50 cc. Each 10 cc contains 5 Gm of dextrose in distilled water

**Solution of Dextrose 50% W/V** 50 cc and 100 cc vials  
Each 10 cc contains 5 Gm of dextrose in distilled water



**PACIFIC COAST STERILE SOLUTIONS CO., LOS ANGELES.**

**Dextrose 5% W/V in Distilled Water:** 1,000 cc. bottles  
Each hundred cubic centimeters contains 5 Gm. of dextrose

**Dextrose 10% W/V in Distilled Water:** 1,000 cc. bottles  
Each hundred cubic centimeters contains 10 Gm. of dextrose

**Dextrose 5% W/V in Isotonic Sodium Chloride Solution:** 1,000 cc. bottles. Each hundred cubic centimeters contains 5 Gm. of dextrose and 0.9 Gm. of sodium chloride-U. S. P.

**Dextrose 10% W/V in Isotonic Sodium Chloride Solution:** 1,000 cc. bottles. Each hundred cubic centimeters contains 10 Gm. of dextrose and 0.9 Gm. of sodium chloride-U. S. P.

**PARKE, DAVIS & COMPANY**

**Glaseptic Ampoule Solution Dextrose 50% W/V:**  
10 Gm. in 20 cc.; 25 Gm. in 50 cc.; and 50 Gm. in 100 cc. A solution of dextrose 50 per cent W/V in distilled water.

**READYFLASK, INC.**

**Dextrose 5% (W/V) in Isotonic Solution of Sodium Chloride:** 1,000 cc. Each 100 cc. contains 5 Gm. of dextrose and 0.9 Gm. of sodium chloride-U. S. P.

**SCHERING & GLATZ, INC.**

**Sterisol Ampoules Dextrose 5% W/V in Distilled Water:** 250 cc., 500 cc., and 1,000 cc. Each 100 cc. contains 5 Gm. of dextrose

**Sterisol Ampoules Dextrose 10% W/V in Distilled Water:** 250 cc., 500 cc., and 1,000 cc. Each 100 cc. contains 10 Gm. of dextrose.

**Sterisol Ampoules Dextrose 20% W/V in Distilled Water:** 250 cc., 500 cc., and 1,000 cc. Each 100 cc. contains 20 Gm. of dextrose.

**Sterisol Ampoules Dextrose 25% W/V in Distilled Water:** 250 cc., 500 cc., and 1,000 cc. Each 100 cc. contains 25 Gm. of dextrose.

**Sterisol Ampoules Dextrose 2½% W/V in Isotonic Solution of Sodium Chloride:** 250 cc., 500 cc. and 1,000 cc. Each 100 cc. contains 2.5 Gm. of dextrose and 0.90 Gm. of sodium chloride.

**Sterisol Ampoules Dextrose 5% W/V in Isotonic Solution of Sodium Chloride:** 250 cc., 500 cc. and 1,000 cc. Each 100 cc. contains 5 Gm. of dextrose and 0.90 Gm. of sodium chloride

**Sterisol Ampoules Dextrose 10% W/V in Isotonic Solution of Sodium Chloride:** 250 cc., 500 cc. and 1,000 cc. Each 100 cc. contains 10 Gm. of dextrose and 0.90 Gm. of sodium chloride

**Sterisol Ampoules Dextrose 20% W/V in Isotonic Solution of Sodium Chloride** 250 cc 500 cc and 1 000 cc  
Each 100 cc contains 20 Gm of dextrose and 0.90 Gm of sodium chloride

**Sterisol Ampoules Dextrose 25% W/V in Isotonic Solution of Sodium Chloride** 250 cc 500 cc and 1 000 cc  
Each 100 cc contains 25 Gm of dextrose and 0.90 Gm of sodium chloride

#### SHARP & DOHME INC

**Ampoules Solution Dextrose (50% W/V)** 20 cc 50 cc and 100 cc  
Each 10 cc contains 5 Gm of dextrose in distilled water

#### THE UPJOHN COMPANY

**Dextrose 10% W/V in Distilled Water** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains dextrose 10 Gm

**Dextrose 20% W/V in Distilled Water** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains dextrose 20 Gm

**Dextrose 5% W/V in Lactate Ringer's Solution** 500 cc 1 000 cc and 2 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains dextrose 5 Gm sodium lactate 0.31 Gm sodium chloride 0.6 Gm potassium chloride 0.03 Gm and calcium chloride 0.02 Gm

**Dextrose 10% W/V in Lactate Ringer's Solution** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains dextrose 10 Gm sodium lactate 0.31 Gm sodium chloride 0.6 Gm potassium chloride 0.03 Gm and calcium chloride 0.02 Gm

**Dextrose 5% W/V in Isotonic Solution** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains 5 Gm of dextrose and 0.85 Gm of sodium chloride U. S. P.

**Dextrose 10% W/V in Isotonic Solution** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains 10 Gm of dextrose and 0.85 Gm of sodium chloride

**Dextrose 5% W/V in Ringer's Solution** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains 5 Gm of dextrose 0.7 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.025 Gm of calcium chloride

**Dextrose 10% W/V in Ringer's Solution** 500 cc and 1 000 cc Upjohn Infusion Bottles  
Each hundred cubic centimeters contains 10 Gm of dextrose 0.7 Gm of sodium chloride 0.03 Gm of potassium chloride and 0.025 Gm of calcium chloride

**U. S. STANDARD PRODUCTS Co.**

**Dextrose Solution 50% W/V:** 50 cc. and 100 cc. bottles  
Each 10 cc. contains 5 Gm. of dextrose in distilled water.

**JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED**

**Dextrose Injection, 50% W/V, U. S. P.:** 50 cc. and 100 cc. Each 10 cc. contains 5 Gm. of dextrose in distilled water.

**Chlorides****ISOTONIC SOLUTION OF SODIUM CHLORIDE.**

—Physiological Solution of Sodium Chloride.—Physiological Salt Solution.—Normal Saline Solution. "Contains in each 100 cc. not less than 0.88 Gm. and not more than 0.92 Gm of NaCl." U. S. P.

For description and standards see U. S. Pharmacopeia under *Liquor Sodii Chloridi Isotonicus*.

**Actions, Uses and Dosage.**—Isotonic solution of sodium chloride is the most commonly used saline solution and is generally employed by parenteral injection for the restoration of the body water in dehydration or for temporary replacement of the circulating blood volume. It is not the fluid of choice in the presence of acidosis. On the basis that one third of the extracellular fluid may be lost in severe anhydremia, and that the extracellular fluid represents one fourth of the body weight, such cases would require an amount of isotonic fluid equal to one twelfth of the body weight.

Isotonic solution of sodium chloride is also used in special containers as a diluent for the aspiration, storage and administration of blood plasma obtained by centrifugation or sedimentation of citrated whole blood. For this purpose the plasma is diluted with an equal volume of the solution.

**ABBOTT LABORATORIES**

**Isotonic Solution of Sodium Chloride:** 250 cc., 500 cc., 1,000 cc. and 2,000 cc. bottles. Each 100 cc. contains 0.9 Gm of sodium chloride in distilled water.

**BAXTER LABORATORIES, INC.**

**Isotonic Solution of Sodium Chloride:** 500 cc., 1,000 cc. and 2,000 cc. Vacoliter containers. Each 100 cc. contains 0.90 Gm. of sodium chloride in distilled water.

**Isotonic Solution of Sodium Chloride:** 250 cc in 500 cc Plasma-Vac container. A sterile isotonic solution of sodium chloride contained under reduced pressure of approximately 12 cm of mercury in a specially adapted bottle which can be equipped with a valve to regulate the aspiration of plasma from other containers and may be used to store or administer the diluted plasma.

U. S. patent 2,108,853

**DON BAXTER, INC**

**Isotonic Solution of Sodium Chloride** 500 cc 1 000 cc and 2 000 cc. Vacoliter containers Each 100 cc contains 0.90 Gm of sodium chloride in distilled water

**Isotonic Solution of Sodium Chloride** 250 cc in 500 cc Plasma Vac container A sterile isotonic solution of sodium chloride contained under reduced pressure of approximately 12 cm of mercury in a specially adapted bottle which can be equipped with a valve to regulate the aspiration of plasma from other containers and may be used to store or administer the diluted plasma

U S patent 2 108 853

**CONTINENTAL HOSPITAL LABORATORIES INC**

**Isotonic Solution of Sodium Chloride** 500 cc and 1 000 cc bottles

**CUTTER LABORATORIES**

**Isotonic Solution of Sodium Chloride** 250 cc, 500 cc, 1 000 cc, and 2 000 cc. Saftiflask containers Each 100 cc contains 0.90 Gm of sodium chloride in distilled water

**ENDO PRODUCTS, INC**

**Ampoules Isotonic Solution of Sodium Chloride** 10 cc, 20 cc and 50 cc Each 10 cc contains 0.90 Gm of sodium chloride in distilled water

**HOSPITAL LIQUIDS INC**

**Isotonic Solution of Sodium Chloride** 1 000 cc and 2 000 cc Filtrair containers Each 100 cc contains 0.9 Gm of sodium chloride in distilled water

**PACIFIC COAST STERILE SOLUTIONS Co**

**Isotonic Solution of Sodium Chloride** 1 000 cc bottles Each hundred cubic centimeters contains 0.9 Gm of sodium chloride U S P

**REDAFLASK INC**

**Isotonic Solution of Sodium Chloride** 1 000 cc Each 100 cc contains 0.85 of sodium chloride U S P in distilled water

**SCHERING & GATZ INC**

**Sterisol Ampoules Isotonic Solution of Sodium Chloride** 250 cc, 500 cc, and 1 000 cc Each 100 cc contains 0.90 Gm of sodium chloride in distilled water

**THE UPJOHN COMPANY**

**Isotonic Solution of Sodium Chloride** 500 cc and 1 000 cc Upjohn Infusion Bottles Each hundred cubic centimeters contains 0.85 Gm of sodium chloride in distilled water

**U. S. STANDARD PRODUCTS CO.**

**Isotonic Solution of Sodium Chloride:** 50 cc. and 100 cc. bottles. Each 10 cc contains 0.85 Gm of sodium chloride in distilled water.

**ISOTONIC SOLUTION OF THREE CHLORIDES**

—Ringer's Solution.—“Contains, in each 100 cc., not less than 0.84 Gm. and not more than 0.88 Gm. of NaCl, not less than 25 mg. and not more than 35 mg. of KCl, and not less than 30 mg. and not more than 36 mg. of  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ .” U. S. P.

Certain modifications of this formula have previously been used which include the addition of 0.02 Gm. of magnesium chloride per 100 cc. and/or 0.03 Gm. of sodium bicarbonate per 100 cc. Ringer's solutions containing either of these ingredients are labeled accordingly.

For description and standards see the U. S. Pharmacopeia under *Liquor Chloridorum Trium Isotonicus*.

**Actions and Uses.**—Isotonic solution of three chlorides is used in all forms of dehydration but particularly in cases in which loss of gastrointestinal secretions has resulted from vomiting, diarrheas or fistulas when sodium, potassium and calcium have been diminished. It is also used in acidosis or alkalosis for improvement of circulation and stimulation of renal activity.

**Dosage.**—Isotonic solution of three chlorides is injected by all parenteral routes according to the extent of the loss of the cations present in the solution and the extracellular body fluid.

**ABBOTT LABORATORIES**

**Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc bottles. Each 100 cc. contains 0.86 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.033 Gm. of calcium chloride.

**BAXTER LABORATORIES, INC.**

**Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. Vacoliter containers. Each 100 cc. contains 0.86 Gm. of sodium chloride, 0.03 Gm. potassium chloride and 0.033 Gm. calcium chloride.

**DON BAXTER, INC.**

**Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. Vacoliter containers. Each 100 cc. contains 0.86 Gm. of sodium chloride, 0.03 Gm. potassium chloride and 0.033 Gm. calcium chloride.

**CONTINENTAL HOSPITAL LABORATORIES, INC.**

**Isotonic Solution of Three Chlorides:** 500 cc. and 1,000 cc. bottle. Each 100 cc. contains 0.86 Gm. of sodium chloride, 0.03 Gm. of potassium chloride and 0.033 Gm. of calcium chloride.

## HOSPITAL LIQUIDS, INC.

**Isotonic Solution of Three Chlorides.** 500 cc., 1 000 cc and 2 000 cc. Filtrax containers. Each 100 cc contains 0.86 Gm of sodium chloride, 0.03 Gm of potassium chloride and 0.033 Gm of calcium chloride.

## THE UPJOHN COMPANY

**Ringer's Solution:** 500 cc and 1 000 cc Upjohn Infusion Bottles. Each hundred cubic centimeters contains 0.7 Gm of sodium chloride, 0.03 Gm of potassium chloride and 0.025 Gm of calcium chloride.

## Sodium Citrate

**SODIUM CITRATE**—“Sodium citrate which dried to constant weight at 150° C., contains not less than 99 per cent of  $C_6H_5OH(COONa)_3$ .”—U. S. P.

For description and standards see the U. S. Pharmacopeia under Sodium Citras and Liquor Sodium Citratis Anticoagulans and the National Formulary under Liquor Sodium Citratis.

**Actions, Uses and Dosage**—Sodium citrate is generally employed in aqueous solution or in isotonic solution of sodium chloride as an anticoagulant for the indirect transfusion of blood. The concentration of such solutions varies from 2½ to 4 per cent of sodium citrate and 10 cc of this strength is ordinarily used for admixture with each 90 cc. to 100 cc of whole blood. This provides a concentration of sodium citrate in the resultant mixture sufficient to prevent coagulation for about forty eight hours. Solutions are available (1) in ampula for addition to receptacles used to receive blood from the donor by the open technic and (2) in special vacuum containers or containers with a rubber bulb attachment for the development of negative pressure, designed to aspirate the donor's blood, and for its administration to the recipient by a closed technic or the preparation of plasma by sedimentation or centrifugation. In either case the blood is added slowly to the required quantity of sodium citrate solution with continuous stirring or gentle shaking.

## ABBOTT LABORATORIES

**Sodium Citrate Solution 3%, W/V:** 50 cc in 500 cc bottle. A sterile 3 per cent solution of sodium citrate in distilled water contained in a specially adapted bottle which can be equipped with an accompanying rubber bulb attachment to assist the inflow of liquids and can be used to administer the citrated blood to the recipient by gravity flow.

## BAXTER LABORATORIES, INC.

**Sodium Citrate 4%, W/V in Distilled Water:** 25 cc and 50 cc in Cettin Vac containers. A sterile 4 per cent solution of sodium citrate in distilled water.

**Sodium Citrate 4% W/V in Distilled Water:** 50 cc. in Transluso-Vac containers. A sterile 4 per cent solution of sodium citrate in distilled water.

GEORGE A. BREON & COMPANY, INC.

**Ampul Solution Sodium Citrate 2½% W/V:** 50 cc. A sterile solution containing in each cubic centimeter sodium citrate-U. S. P. 0025 Gm.

CONTINENTAL HOSPITAL LABORATORIES, INC.

**Sodium Citrate 2½% W/V in Isotonic Solution of Sodium Chloride:** 70 cc. in a 1 liter vacuum flask. A sterile 2.5 per cent solution of sodium citrate in isotonic solution of sodium chloride contained in a vacuum flask designed to permit aspiration of blood from the donor and subsequent administration of citrated whole blood to the recipient by gravity flow.

HOSPITAL LIQUIDS, INC.

**Sodium Citrate 2½% W/V in Isotonic Sodium Chloride Solution:** 35 cc. and 70 cc. in Filtrair Haemovac containers of 720 cc. capacity. A sterile distilled water solution of sodium citrate 2.5 per cent (W/V) and sodium chloride 0.9 per cent (W/V) contained under reduced pressure of not more than 100 mm. of mercury in a specially adapted bottle designed for the aspiration, citration and gravity administration of 250 cc. or 500 cc. of whole blood in indirect transfusion by a closed technique.

**Sodium Citrate 2½% W/V in Isotonic Sodium Chloride Solution:** 35 cc. in Filtrair Centrifuge Haemovac container of 315 cc. capacity. A sterile distilled water solution of sodium citrate 2.5 per cent (W/V) and sodium chloride U. S. P. 0.9 per cent (W/V) contained under reduced pressure of not more than 100 mm. of mercury in a specially adapted bottle designed for the aspiration, citration and centrifugation of 250 cc. of whole blood in the preparation of blood plasma.

**Sodium Citrate 2½% W/V in Isotonic Sodium Chloride Solution:** 35 cc. and 70 cc. in Filtrair Sedimentation Haemovac containers of 720 cc. capacity. A sterile distilled water solution of sodium citrate 2.5 per cent (W/V) and sodium chloride U. S. P. 0.9 per cent (W/V) contained under reduced pressure of not more than 100 mm. of mercury in a specially adapted bottle designed for the aspiration, citration and storage during the sedimentation of 250 cc. or 500 cc. of whole blood in the preparation of plasma. The container may also be used for the gravity administration of the citrated whole blood in indirect transfusion by a closed technique.

U. S. trademark (Haemovac) 379,042

THE LAKESIDE LABORATORIES, INC.

**Ampuls Sodium Citrate 2.5% (W/V):** 50 cc

THE UPJOHN COMPANY

**Solution Sodium Citrate  $2\frac{1}{2}\%$ , W/V** 50 cc ampuls  
A sterile solution containing in each cubic centimeter sodium citrate 0.025 Gm

**Sodium Lactate**

**SODIUM *r*-LACTATE ONE-SIXTH MOLAR** — A solution of sodium *r* lactate one sixth molar (187 per cent W/V)

**Actions and Uses** — Sodium *r* lactate one sixth molar is approximately isotonic with the blood and is used in the treatment of acidosis (as such or combined with Ringer's solution) and for the purpose of alkalinizing the urine (for instance in the treatment of acute urinary tract infections with sulfanilamide, in the treatment of transfusion reactions with hemoglobinuria). This solution is not indicated in the acidosis associated with congenital heart disease with persistent cyanosis.

**Dosage** — Administered subcutaneously or intravenously

Intr	"	"
grea	"	"
mini	"	"
calci	"	"
per	"	"
cent	"	"
liter	"	"
suffi	"	"
per	"	"

**Tests and Standards** —

Sodium *r* lactate solution occurs as a clear colorless odorless liquid possessing a slightly saline test. The *ph* of the solution when determined with a glass electrode is between 4.8 and 6.0. Moisten a clean platinum wire with the solution and hold in a nonluminous flame; an intense yellow color is imparted to the flame. To 5 cc. of sodium *r* lactate solution add 1 cc. of diluted sulfuric acid and 1 cc. of potassium permanganate solution and heat; acetaldehyde is evolved. To a 5 cc. portion of sodium *r* lactate solution add 1 cc. of diluted nitric acid and 1 cc. of a clear nitrate solution; no turbidity or precipitate occurs. Ten cc. samples of sodium *r* lactate solution yield negative tests for arsenic and heavy metals when tested according to the U. S. P. XI methods.

A 50 cc. sample of sodium *r* lactate solution remains colorless after the addition of 3 drops of phenolphthalein solution and between 15 and 25 cc. of tenth normal alkali as necessary to turn the solution pink.

Transfer exactly 10 cc. of sodium *r* lactate solution to a platinum crucible and evaporate to dryness. Heat the residue gently and then gradually raise the temperature until the mass is carbonized, but do not exceed a dull red heat. Cool the mass and moisten with a drop of distilled water. Age a few hours to dull redness and repeat the procedure until the residue is white. Transfer the cooled residue and its contents to a beaker and dissolve the residue in 50 cc. of water. Treat with tenth normal acid using methyl orange as indicator; not more than 17.5 nor less than 16.5 cc. of tenth normal acid is required. Transfer a 25 cc. sample of sodium *r* lactate solution to a tared platinum dish and add 1 cc. of sulfuric acid. Evaporate to dryness and weigh the residue. It should have the weight of the residue not less than 0.1500 gm. and not more than 0.2500 gm.



## ABROTT LABORATORIES

**Solution Sodium-*r*-Lactate**  $\frac{1}{6}$  Molar: 500 cc. and 1,000 cc bottles. A sterile solution of sodium *r*-Lactate one-sixth molar (1.87% W/V) in distilled water

## BAXTER LABORATORIES, INC.

**One-Sixth Molar Sodium *r*-Lactate Solution:** 500 cc and 1,000 cc. Vacoliter containers

## DON BAXTER, INC.

**One-Sixth Molar Sodium *r*-Lactate Solution:** 500 cc and 1,000 cc. Vacoliter containers

## E. L. LITTLE &amp; COMPANY

**Ampoules Sodium *r*-Lactate Solution One Molar:** 40 cc and 100 cc. Each 10 cc. contains 1.12 Gm. of sodium *r*-lactate. Each 1 volume of this solution must be diluted with 5 volumes of sterile distilled water to obtain a sterile approximately isotonic solution equivalent in strength to sodium *r*-lactate one-sixth molar.

## THE UPJOHN COMPANY

**Sodium Lactate (Racemic)  $\frac{1}{6}$  Molar (1.87% W/V):** 500 cc. and 1,000 cc. Upjohn Infusion Bottles. Each hundred cubic centimeters contains 1.87 Gm of sodium *r*-lactate in sterile distilled water.

## LACTATE RINGER'S SOLUTION

isotonic aqueous solution cor-  
ride, 06 Gm.; potassium chlo-  
002 Gm., and sodium lactate,  
lactate is prepared by neutralizing lactic acid with a solution  
of sodium hydroxide. Certain modifications of this formula have  
been used, which include the addition of 002 Gm of mag-  
nesium chloride and/or 003 Gm. of sodium bicarbonate per 100  
cubic centimeters. Lactate Ringer's solution containing either  
of these ingredients is labeled accordingly.

**Actions and Uses**—Lactate Ringer's solution has essentially the same use as isotonic solution of sodium chloride, and more particularly isotonic solution of three chlorides. As is the case with the other salt solutions, it is approximately isotonic with body fluids and may be accompanied with various percentages of dextrose for the purpose of supplying nourishment by vein. Lactate Ringer's solution is designed primarily for supplying certain mineral needs of the body and for the purpose of maintaining or helping to maintain buffer balances.

**Dosage**—Same as for isotonic solution of three chlorides (Ringer's solution)

*Tests and Standards—*

Lactate Ringer's solution occurs as a clear colorless odorless solution, possessing a slightly saline taste. The specific gravity is from 1.006 to 1.007 at 25 C and the  $pH$  is not below 5.0 nor above 7.5. Twenty-five cc of the solution concentrated to 10 cc conforms to the U. S. P. XI test for heavy metals.

Transfer 1 cc of lactate Ringer's solution drop by drop to 4 cc of sulfuric acid contained in a test tube and keep cool by agitation in cold water. Place the test tube and contents in the steam bath for two minutes, remove the test tube and cool the contents well, add cautiously 1 cc of a saturated aqueous gumaccol solution, a rose color develops.

Evaporate a 20 cc portion of lactate Ringer's solution in a beaker

Transfer 9 cc of a mixture of a potassium dichromate solution and a 10% solution of sodium carbonate to a 100 cc volumetric flask and add 1 cc of the solution to be tested. The solution should be colorless or very faintly pink. If the solution is pink, it indicates the presence of iron.

0.258 Gm of potassium dichromate (7.6237 Gm of  $K_2Cr_2O_7$  per liter) to a 500 cc Erlenmeyer flask add 25 cc of lactate Ringer's solution and 60 cc of an aqueous solution of sulfuric acid (40%  $H_2SO_4$ ). Place the flask and contents in a water bath at 70 C. Stopper the flask when the solution attains the temperature of water bath and keep the flask and contents in the water bath for one hour. Cool the solution, add 200 cc of water and 8 cc of potassium iodide solution (10% KI). Stopper the flask and mix the contents well. Allow to stand for 5 minutes.

Titrate the solution with 0.005 N sodium thiosulfate solution. The solution should be colorless or very faintly pink. If the solution is pink, it indicates the presence of iron. The solution should be colorless or very faintly pink. If the solution is pink, it indicates the presence of iron. The solution should be colorless or very faintly pink. If the solution is pink, it indicates the presence of iron.

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**ABBOTT LABORATORIES**

**Lactate Ringer's Solution:** 500 cc. and 1,000 cc. bottles  
 Each hundred cubic centimeters contains sodium lactate 0.31 Gm.,  
 sodium chloride 0.6 Gm., potassium chloride 0.03 Gm. and  
 calcium chloride 0.02 Gm.

**BAXTER LABORATORIES, INC.**

**Lactate-Ringer's Solution:** 500 cc. and 1,000 cc. Vacoliter  
 containers

**DON BAXTER, INC.**

**Lactate Ringer's Solution:** 500 cc. and 1,000 cc. Vacoliter-  
 containers.

**CONTINENTAL HOSPITAL LABORATORIES, INC.**

**Lactate Ringer's Solution:** 500 cc. and 1,000 cc. bottles

**ELI LILLY & COMPANY**

**Ampoules Lactate Ringer's Solution 25 Times Concen-**  
**trated:** 10 cc. and 20 cc. When 1 volume of the solution is  
 diluted with 24 volumes of sterile distilled water. The diluted  
 solution is equivalent in strength to lactate Ringer's solution-  
 N N R.

**THE UPJOHN COMPANY**

**Lactate Ringer's Solution:** 500 cc. and 1,000 cc. Upjohn  
 Infusion Bottles Each hundred cubic centimeters contains  
 sodium lactate 0.31 Gm., sodium chloride 0.6 Gm., potassium  
 chloride 0.04 Gm. and calcium chloride 0.02 Gm. in redistilled  
 water.

## CHAPTER XIX

### PHARMACEUTIC AND THERAPEUTIC AIDS

**CHLORINATED PARAFFIN** — Chlorococane — 'A liquid paraffin which has been treated with chlorine' *N F*

For description and standards see the National Formulary under Paraffinum Chlorinatum

*Actions and Uses* — The chlorine of chlorinated paraffin is therapeutically without action. Chlorinated paraffin is used as a solvent for dichloramine T. With it solutions containing up to 8 per cent may be prepared. The high viscosity of the oil prevents its being readily sprayed with a hand spray; the addition of about 10 per cent carbon tetrachloride will reduce the viscosity so that it can be readily sprayed in an ordinary oil atomizer.

**GELATIN COMPOUND PHENOLIZED** — A mixture composed of gelatin 14 per cent, zinc oxide 5.5 per cent, propylene glycol 39 per cent, distilled water 40 per cent, containing 1.5 per cent of phenol.

*Actions and Uses* — Gelatin compound phenolized is used in the preparation of bandages to cover chronic ulcers and unhealed secondary burns and in the preparation of pressure bandages for varicose veins when surgical treatment is not necessary.

*Dosage* — For use the preparation is heated until it becomes liquid and is applied with a brush. Over this a spiral bandage is applied and another layer of the preparation brushed on; this is repeated until a total thickness of three layers of the bandage and four of the preparation has been applied.

SHARP & DOHME, INC.

Gelatine Compound Phenolized bulk

**PARRESINE** — A mixture composed of paraffin (melting point 48 to 49 C) from 94 to 96 per cent, gum elemi from 0.20 to 0.25 per cent, Japan wax from 0.40 to 0.50 per cent, asphalt from 0.20 to 0.25 per cent, and eucalyptol 2 per cent. To this mixture is added from 0.5 to 1.0 per cent solution of alkanin in eucalyptol and a minute quantity of gentian violet, these being employed to bring the product to a standard color. Marketed only in the form of Parresined Lace Mesh Surgical Dressing.

*Actions, Uses and Dosage* — Non absorbent protective use for the preparation of Parresined Lace Mesh Surgical Dressing.

ABBOTT LABORATORIES

**Parresined Lace Mesh Surgical Dressing** — Net mesh gauze impregnated with and containing from 45 to 50 per cent of parresine.

U. S. trademark 117,676

**BROMURAL.**— $(\text{CH}_3\text{CH}(\text{CH}_3)\text{CHBr.CO})\text{HN.CO.NH}_2$ —2-monobromisovalerylurea, obtained by the interaction of urea with bromisovaleryl bromide.

*Actions and Uses.*—Bromural is a sedative which produces sleep in mild cases of insomnia without markedly affecting the circulation or respiration. All action by bromural is said to cease after from three to five hours. In many cases, however, the sleep caused by the preparation continues beyond the limits of its action. It is useful as a sedative and for the purpose of inducing sleep in functional nervous disease. Bromural is not effective in cases of insomnia associated with pain, cough, angina pectoris or delirium.

*Dosage.*—As a sedative, 0.3 Gm., three times daily; as a hypnotic at bedtime, 0.6 Gm., which dose may be repeated if advisable during the night, after three to four hours.

*Tests and Standards.*—

Bromural forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily in cold water. It sublimates on heating and melts at from 147 to 149 C.

Bromural can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromine may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for a bromide with silver nitrate solution. On heating the alcoholic solution of bromural with sodium ethylate for several hours on the water bath, sodium bromide will precipitate. If this is filtered off and the filtrate evaporated, a crystalline mass remains which can be recrystallized from water. This is dimethylacrylic acid, melting at 280 C. If 1 Gm. of bromural is boiled for about one minute with 10 per cent solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid is then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oily fluid 1-bromisovaleric acid, which has the specific odor of valeric acid, will remain. The biuret reaction cannot be obtained. On melting bromural and adding concentrated sodium hydroxide solution and copper sulfate, no color reaction will take place.

**BILHUBER-KNOLL CORP.**

Tablets Bromural: 0.3 Gm.

U. S. patent 914,318 (March 9, 1909; expired) U. S. trademark 61,165.

**CARBROMAL.**—Bromdiethylacetylurea — For description and standards see the National Formulary under Carbromalum.

*Actions and Uses.*—Carbromal is said to be an efficient and prompt sedative, reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasant by-effects and sequelae.

Carbromal is stated to be useful as a sedative and mild hypnotic in neurasthenia, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases.





only in degree. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acyls (diacetyl morphine), the narcotic effects are stronger than with codeine and the tetanic action is weaker than with morphine.

*Actions and Uses*—The central actions of all these morphine derivatives are qualitatively identical but they present quantitative differences which have some practical importance.

*Morphine* produces the strongest narcotic analgesic hypnotic and intestinal effects and the weakest stimulation. It causes the greatest derangement of digestion. It and diacetyl morphine are most liable to induce a habit.

*Codeine* (methyl morphine) is less narcotic, less constipating and less apt to induce tolerance and habit. It is therefore especially valuable in cough or in other conditions in which the sedative action must be continued for some time and in patients who do not tolerate morphine.

*Ethyl Morphine* seems to stand intermediate between morphine and codeine in all respects. The hydrochloride is used as a sedative but mainly for its special action on the conjunctiva.

*Diacetyl Morphine* (heroin) closely approaches morphine of which it shares all the disadvantages and over which it has no important advantage. It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration but that the inspirations are deepened and more powerful so that the alveolar air is more effectively ventilated. Independent workers however have shown that there is no real difference from morphine in these respects. It is now generally conceded that diacetyl morphine is as effective as morphine in cough but not more so that it is rather less effective against dyspnea and that it is more liable to produce habit and toxic effects.

## “ . . . HYDROCHLORIDE —

Hydrochloride—Dihydro-  
essentially from morphine  
hydroxyl groups of the latter

has been replaced by a ketone group and the adjacent double bond has been removed by hydrogenation.

For description and standards see the U. S. Pharmacopoeia under Dihydromorphinone Hydrochloridum and Tabellae Dihydromorphinone Hydrochlorid.

*Actions and Uses*—The base dihydromorphinone is closely allied both chemically and pharmacologically to morphine having the analgesic property of morphine as well as its action on the respiratory system. Its action on the intestine is probably less marked than is that of morphine. It is more toxic than morphine and is clinically effective in doses which are considerably smaller than are necessary with that alkaloid. It has been



shown experimentally and clinically that dihydromorphinone is powerfully analgesic and that, like morphine, it can depress the respiratory mechanism profoundly. At the same time, the experimentally established ratio between effective doses of morphine and dihydromorphinone for the production of desirable effects is not materially different from the ratio between their toxic doses. Clinical trial has not shown that dihydromorphinone is free from tolerance and addiction-evoking properties, and, while side actions, such as nausea, vomiting and constipation seen to occur less frequently than with morphine, the prolonged administration of dihydromorphinone should be undertaken with as much caution as would be exercised with morphine itself. Dihydromorphinone hydrochloride comes within the scope of the federal narcotic regulations.

**Dosage**—As a sedative and for the relief of pain, the usual oral dose is 2.5 mg. ( $\frac{1}{48}$  grain); in mild pain or cough, 1.3 mg ( $\frac{1}{48}$  grain) may be given orally. The customary hypodermic dose is 2 mg ( $\frac{1}{48}$  grain). Clinically the dose necessary to produce analgesia is about one-fifth that of morphine.

#### BILHURER-KNOX, CORP.

**Ampules Solution Dilaudid Hydrochloride:** 1.1 cc Each cubic centimeter contains dihydromorphinone hydrochloride, 2 mg. in isotonic solution of sodium chloride.

**Dilaudid Hydrochloride Compounding Tablets:** 16 mg These tablets, each many times the average dose, are for use in compounding only.

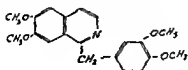
**Hypodermic Tablets Dilaudid Hydrochloride:** 1 mg. 2 mg., 3.2 mg and 4 mg

**Tablet Dilaudid Hydrochloride:** 25 mg

**Dilaudid Hydrochloride, Rectal Suppositories:** 25 mg dihydromorphinone hydrochloride in cacao butter base

German patent 380,919 (1923) U S trademark 298 197

**PAPAVERINE.**—Papaverina.— $C_{20}H_{21}O_4N$ —An alkaloid obtained from opium, belonging to the benzyl isoquinoline group (that is, it is not a morphine derivative)



**Actions and Uses**—Pal found that papaverine relaxes smooth muscle in general, although different organs are affected in a varying degree

Papaverine is most effective in hypertonic conditions while it does not interfere materially with the normal movements for instance, of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither tolerance nor habituation has been reported. These actions have prompted its use, with reported success, in various spasmodic conditions of the smooth muscles. Pal recommends it especially in all kinds of gastric and intestinal spasms (also for the diagnosis of pyloric spasm), in biliary colic, and in bronchial spasm. Of more doubtful value is its employment in pertussis, hyperemesis, and vascular spasm—angina pectoris, acute uremia and eclampsia. It is ineffective in chronic hypertension. The local anesthetic action, with vasodilatation has been used against rhino asthma, to treat bronchial asthma and to mitigate the pain of irritant injections.

**Dosage**—The oral and hypodermic single dose is from 0.03 to 0.08 Gm. daily dose to 0.5 Gm. Single doses of even 1 Gm. are said to be nontoxic.

#### *Tests and Standards*—

Papaverine occurs in fine white rhombic prisms or needles or sometimes in scales. It is odorless and tasteless. It is nearly insoluble in cold water, slightly soluble in alcohol, ether, chloroform and benzene if cold, somewhat more soluble in these liquids when hot but leposited by them on cooling and soluble in warm petroleum ether and in acetone. It melts at 147 C.

If about 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of diluted hydrochloric acid and a few drops of potassium ferricyanide solution is added a lemon yellow precipitate of papaverine ferricyanide should form at once (*distinction from other opium alkaloids*). If about 0.001 Gm. of papaverine is dissolved in 0.1 cc. of sulfuric acid containing in each cubic centimeter 1 drop of formaldehyde solution, a colorless or, at most a faintly yellowish green solution should be produced. This gradually changes to deep rose and finally becomes brown (*distinction from morphine and its esters which give purple or violet colors*). If 0.01 Gm. of papaverine is dissolved in 0.2 cc. of sulfuric acid the solution should not be colored more deeply than a very faint pink or brown (*limit of cryptopine thebaine or of other organic impurities*). If 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of hydrochloric acid a few drops of a saturated aqueous solution of iodine acid added, and the mixture shaken with chloroform the chloroform layer should not be colored violet (*morphine*).

If from 0.2 to 0.3 Gm. of papaverine is weighed dissolved in 20 cc. of warm water containing a few drops of diluted hydrochloric acid the solution cooled 1 cc. of freshly prepared potassium ferricyanide solution added the mixture agitated allowed to stand overnight and filtered the filtrate made alkaline with ammonia water shaken with several successive portions of ether the ether solutions combined washed with water evaporated the residue dried at 100 C. and weighed the weight should not amount to more than 2 per cent of the weight taken (*limit of foreign opium alkaloids*).

**PAPAVERINE HYDROCHLORIDE**—The hydrochloride of an alkaloid obtained from opium.  $\text{N} \text{ I}$

For description and standards see the National Formulary under *Papaverinae Hydrochloridum*.

**Actions, Uses and Dosage**—See preceding article *Papaverine*.

## Sulfonmethanes

Two analogous compounds formed by the substitution of sulfone radicals in methane have been applied in therapeutics. The first, sulfonmethane-N. F. (sulfonal) is diethylsulfon-dimethylmethane; the second, sulfonethylmethane-N. F. (trional) is diethylsulfonmethylethylmethane. The latter has been generally given the preference.

Sulfonmethane is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established; sulfonethylmethane is somewhat more soluble than sulfonal and acts more quickly. Both drugs are preferably given in hot liquids; and in the case of sulfonmethane, the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Sulfonethylmethane is usually effective in an hour or two.

The sulfonmethanes in therapeutic doses produce sleep without noticeable effect on the circulation or respiration. In larger doses, acute poisoning occurs, evidenced by disturbances of the digestive organs, the metabolism and the nervous system. When administered for too long a period, emulsion is likely to occur, producing a condition of chronic poisoning which terminates fatally in a large percentage of cases. In such cases, hematoporphyrin derived from hemoglobin turns the urine pink or red. This should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

**Dosage**—The usual dose of either sulfonmethane or sulfonethylmethane is 1.0 Gm. with a maximum of 2 Gm. for the first and 4 Gm. for the second. When these drugs are used frequently, the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematoporphyrin.

**SULFONMETHANE.**—Sulfonal—For description and standards see the National Formulary under Sulfonmethanum.

**Actions, Uses and Dosage.**—See preceding article, Sulfonmethanes.

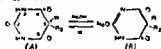
**SULFONETHYLMETHANE.**—Diethylsulfonmethylethylmethane—For description and standards see the National Formulary under Sulfonethylmethanum.

## Barbituric Acid Derivatives

Barbital (diethylbarbituric acid), which was introduced under the name of "veronal," is chemically related to urea and the carbamate hypnotics



The ethyl groups may be replaced by other alkyl or aryl radicals to form a large number of derivatives of the general structure indicated in 'A'



The following compounds or their salts are described in N N R

## COMPOUNDS

## SUBSTITUENTS

	R <sub>1</sub>	R <sub>2</sub>	Other Substituent
Barbital	Ethyl	Ethyl	
Amytal	Ethyl	Isoamyl	
Ipral	Ethyl	Isopropyl	
Neonal	Ethyl	n Butyl	
Ortal	Ethyl	n Hexyl	
Leptothal	Ethyl	1 Methylbutyl	2 Thio
Pentobarbital	Ethyl	1 Methylbutyl	
Phenobarbital	Ethyl	Phenyl	
Phanodorn	Ethyl	Cyclohexenyl	
Evipal	Methyl	Cyclohexenyl	1 Methyl
Alurate	Allyl	Isopropyl	
Dial	Allyl	Allyl	
Seconal	Allyl	1 Methylbutyl	
Sandoptal	Allyl	Isobutyl	
Noatal	β Bromallyl	Isopropyl	
Pernoston	β Bromallyl	Butyl	

The compounds (acids) listed are only sparingly soluble in water, but freely soluble compounds of the general structure indicated in 'B' are formed in the presence of sodium hydroxide e g, barbital sodium U S P

**Actions and Uses**—Barbital and its derivatives are effective sedatives and hypnotics, and are used as such in simple insomnia, hysteria, neurasthenia, thyroid disease and chorea, in epilepsy in the intervals between the seizures, in mental disturbances and in impending delirium tremens. They also augment the action of analgesics such as aminopyrine, acetophenetidin and acetylsalicylic acid, and they are used in combination with these analgetics for the relief of pain, especially of neuralgic character. The therapeutic effects are exerted on the higher centers of the brain, and therapeutic doses do not usually cause any apparent injury to the heart, circulation, or kidneys.

They are decidedly more actively hypnotic and somewhat more analgetic than chloral hydrate; they do not produce local irritation and the taste is not disagreeable. The margin between the ordinary therapeutic dose and the toxic dose is somewhat wider than that with chloral hydrate and small therapeutic doses have little effect on the blood pressure and respiration. Several of the derivatives of barbital are more actively hypnotic than the parent substance and may be preferred, especially as a sedative, but there is no satisfactory evidence that the margin between the therapeutic and toxic doses of these derivatives is significantly wider than in the case of barbital itself. The action is somewhat slower than with chloral hydrate but more rapid than with sulfonmethane. In

the absence of pain, small doses usually induce sleep within half an hour. The sleep lasts for four to eight hours, varying with individuals, with the drug used and with the dose. The patient generally awakens refreshed, but occasionally there are lassitude, vertigo, headache, nausea and diarrhea on the following day even after moderate doses. In some patients barbital and its derivatives produce restlessness and excitement, and these agents should not be used for such patients. Skin eruptions are sometimes observed. Fatal collapse (by peripheral paralysis of the blood vessels) has occurred after relatively small doses. Toxic doses cause lowered body temperature, depression of the respiration and circulation, and feeble heart beat. There is long-continued stupor, sometimes interrupted by excitement. The condition has been confused with uremia, epidemic encephalitis and opium poisoning. The slower the excretion of the various members of this group, the more lasting is the action, and with very slow excretion ordinary doses may produce cumulative toxic effects after some time. Death results from paralysis of respiration. It is therefore safer to intermit the administration at least weekly. Continued use may lead to habitual addiction. Barbital preparations are usually administered orally or rectally. Barbital and the acid derivatives are slightly soluble in water; the readily soluble sodium salts have closely similar actions after they enter the circulation.

In emergencies, when prompt action is imperative, when oral or rectal administration is not feasible, and in other carefully selected instances one of the soluble preparations may be injected intravenously. Certain of the briefly acting soluble barbiturates are injected intravenously as general anesthetics in selected cases, but the method is not devoid of danger. It

compounds may also be used to induce anesthesia prior to its continuance by other means, such as gaseous anesthetics, but such technic is by no means suitable as a routine measure. It should be used when the patient is exceedingly exhausted, when the patient indicates that fairly large doses are necessary to relieve the conditions arising from poisoning, when the more common paralysis has resulted.

**ALURATE.**—5-Allyl-5-isopropylbarbituric acid — Allyl-isopropyl-malonylurea —  $C_{10}H_{14}O_2N_2$  — M. W. 210.23



**Actions and Uses.**—The actions and uses of alurate are essentially similar to those of barbital, but alurate is more active than barbital and is used in correspondingly smaller doses.

Fractional doses are used as a sedative and larger doses as a hypnotic

**Dosage**—For mild cases of insomnia 0.065 Gm may be administered at bedtime. In obstinate cases 0.13 Gm may be given.

### Tests and Standards—

Alurate occurs as a fine white, odorless crystalline powder, with a slightly bitter taste, completely soluble in alcohol, chloroform and ether, very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Alurate melts at 140 to 141.5°C.

Place about 0.3 Gm of alurate in a glass stoppered cylinder, add a mixture of 1 cc of normal sodium hydroxide solution and 5 cc of water, shake the contents for one minute, filter through paper and if mercuric chloride excess of ammonia solution a white water. Boil about 10 minutes.

It is decomposed with the evolution of ammonia. Dissolve about 0.1 Gm of alurate in 1 cc of sulfuric acid; not more than a slight yellow color results. Place about 1 Gm of alurate in a 25 cc glass stoppered cylinder, add 10 cc of water, shake the mixture for one minute, filter through paper and divide into two portions, to one portion add 1 cc of acetic acid and 0.5 cc of a saturated bromine water; an immediate discoloration occurs, to the other portion add 0.1 cc of tenth normal potassium permanganate solution; a yellow color appears immediately, turning to brown.

Boil about 0.5 Gm of alurate with 50 cc of water for two minutes; no odor develops, cool and filter; separate portions of 10 cc each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (*chloride*), no turbidity with 1 cc of diluted nitric acid and 1 cc of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Incinerate about 1 Gm of alurate accurately weighed; there is not more than 0.1 per cent residue. Dissolve about 0.5 Gm of alurate, accurately weighed in 25 cc of previously neutralized alcohol. Dilute with an equal volume of water previously boiled to remove carbon dioxide and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator; the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent allylpropylbarbiturate acid.

### HOFFMANN-LAROCHE, INC

**Alurate (Powder):** bulk

**Tablets:** Alurate. 0.065 Gm

**Elixir Alurate:** Contains alurate approximately 0.9 Gm per hundred cubic centimeters in a palatable elixir containing alcohol, 20 per cent.

U. S. patent 1,444,802 (Feb. 13, 1923; expired 1940). U. S. trademark 230,059.

**SODIUM ALURATE**—Sodium-5-allyl-5-isopropyl barbiturate. The monosodium salt of 5-allyl-5-isopropyl malonylurea.  $C_{10}H_{15}O_3N_2Na$ —M. W. 232.22.

**Actions and Uses**—The same as those for alurate. The soluble sodium salt is intended for oral or rectal administration.

particularly as preanesthesia medication. Sodium alurate may also be used in other cases in which large individual doses are required.

**Dosage.**—The average preoperative dose is 10 mg. per kilogram of body weight. One third of the calculated dose is given ten or twelve hours prior to operation (usually the evening before); the remainder, two hours before operation. Experience is necessary in the use of these large dosages, as the amount of the drug must be adjusted to the individual patient in order to avoid undesirable reactions.

### Tests and Standards—

Sodium alurate is a white microcrystalline, hygroscopic, odorless powder, with a slightly bitter taste; very soluble in water; very slightly soluble in alcohol; practically insoluble in ether. An aqueous solution of sodium alurate is alkaline to litmus.

Dissolve about 0.5 Gm. of sodium alurate in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the resultant allyl isopropyl barbituric acid on a filter, wash and dry at 90 C.; it melts at 139 to 140 C. Incinerate about 1 Gm. of sodium alurate; the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of sodium alurate with 5 cc. of a 25 per cent sodium hydroxide solution; it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of sodium alurate in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution; a white precipitate results, soluble in an excess of ammonia water; to the other portion add 5 cc. of silver nitrate solution; a white precipitate results, soluble in an excess of ammonia water.

Dissolve about 0.5 Gm. of sodium alurate in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper; separate portions of

alurate, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.; the residue does not exceed 0.2 per cent (uncombined allylisopropyl barbituric acid).

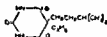
Dry about 1 Gm. of sodium alurate, accurately weighed, at 90 C. for forty-eight hours; the loss in weight should not be less than 4.5 per cent nor more than 7.5 per cent. Transfer about 0.5 Gm. of sodium alurate, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C.; the amount of allylisopropyl barbituric acid corresponds to not less than 90 per cent nor more than 91 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath, to the residue obtained add 5 cc. of sulfuric acid; heat cautiously until the excess of sulfuric acid has been volatilized, repeat twice, using portions of 1 cc. each of sulfuric acid each time, add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weight as sodium sulfate; the percentage of sodium corresponds to not less than 9 per cent nor more than 10 per cent when calculated to the dried substance.

## HOFFMANN-LAROCHE, INC

**Capsules Sodium Alurate**—3½ grains Each capsule is equivalent to approximately 02 Gm (3 grains) of alurate

U S patent 1 444 802 (Feb 13 1923 expired) U S trademark 230 059

**AMYTAL** — 5 Isoamyl 5 ethylbarbituric acid — Isoamyl ethyl malonylurea —  $C_{11}H_{19}O_3N_2$  — M W 226 27



**Actions and Uses**—The actions and uses of amytal resemble those of barbitol. It is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

**Dosage**—It is given orally in tablet form with water or hot milk. As a sedative 0.02 to 0.04 Gm two or three times daily. As a hypnotic 0.1 to 0.3 Gm one half to one hour before sleep is desired. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm being determined by a large number of factors (age etc). It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. As an antispasmodic in tetanus 0.4 to 0.8 Gm may be required to control convulsions.

#### Tests and Standards—

Amytal occurs as a white crystalline odorless powder with a slightly bitter taste, completely soluble in alcohol and ether, very slightly soluble in cold water and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 153–155°C.

Place 0.3 Gm of amytal in a test tube, add 1 cc of water, shake the contents, allow to settle, divide into two portions. To the first portion add 1 cc of silver nitrate solution, a white precipitate results, soluble in 5 cc of ammonia water. Boil 0.5 Gm of amytal with 5 cc of a 25 per cent sodium hydroxide solution; it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm of amytal in 1 cc of sulfuric acid; the solution is colorless (readily carbonizable substances). Boil 0.5 Gm of amytal with 50 cc of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (chloride), no turbidity with 1 cc of diluted nitric acid and 1 cc of barium nitrate solution (sulfate); no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Incinerate about 1 Gm of amytal accurately weighed; the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm of amytal accurately weighed in 25 cc of previously neutralized alcohol dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator; the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isoamyl ethylbarbituric acid.



## ELI LILLY AND COMPANY

## Amytal (Powder): bulk.

U. S. patent 1,514,573 (Nov. 4, 1924; expired). U S trademark 161,125.

Tablets Amytal: 8 mg., 16 mg., 48 mg. and 96 mg.

Elixir Amytal: 0.44 Gm. per hundred cubic centimeters and 0.88 Gm. per hundred cubic centimeters in a vehicle containing alcohol, glycerin, water and aromatics; methenamine is present for the purpose of increasing the solubility of the amytal.

**SODIUM AMYTAL.**—Sodium Isoamylethylbarbiturate—The monosodium salt of 5-isoamyl-5-ethylbarbituric acid— $C_{11}H_{19}O_3N_2Na$ .—M. W. 248.26.

*Actions and Uses.*—The actions and uses of sodium amytal resemble those of barbital. The product is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

*Dosage*—As a potent sedative or hypnotic 0.2 Gm., repeated if necessary at intervals of six hours. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm. being determined by a large number of factors (age, etc.). As an antispasmodic in tetanus, from 0.4 to 0.8 Gm. may be required to control convulsions. It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. In some patients barbiturate derivatives produce restlessness and excitement, and to these patients sodium amytal should not be administered. It may be administered by mouth, or, if necessary, the same dose may be given rectally, in the form of capsules inserted as suppositories or as powder placed in a little water; it should be administered intravenously only in those conditions outlined in the general section on barbituric acid derivatives.

*Tests and Standards*—

Sodium amytal occurs as a white, friable, hygroscopic odorless granular powder with a slightly bitter taste, very soluble in water, freely soluble in alcohol about 1 part in 1 part; practically insoluble in ether.

Dissolve about 0.5 Gm. of sodium amytal in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant isoamyl ethylbarbituric acid on a filter, wash and dry; it melts at 152-155 C. Incinerate about 1 Gm. of sodium amytal; the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of sodium amytal with 5 cc. of a 25 per cent sodium hydroxide solution; it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of sodium amytal in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution, a white precipitate results, soluble in an excess of ammonia, to the other portion add 5 cc. of silver nitrate solution, a white precipitate results, soluble in 5 cc. of ammonia water.

Dissolve about 0.5 Gm. of sodium amytal in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper. Separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (chloride), no turbidity on the addition of 1 cc. of silver nitrate solution (sulfate). To about 0.2 Gm. of sodium amytal in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper; the filtrate yields no coloration or precipitate.

tion on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.2 Gm of sodium amytal to 1 cc of sulfuric acid the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm of sodium amytal accurately weighed to a glass stoppered cylinder add 50 cc of anhydrous ether, stopper and shake the contents for ten minutes, decant the supernatant liquid through filter paper, and repeat twice, using first 25 cc and second 15 cc of ether and utilizing the same filter evaporate the combined filtrate to dryness in a tared beaker and dry to constant weight at 100 C the residue does not exceed 0.2 per cent (*uncombined isoamylethylbarbituric acid*).

Dry about 1 Gm of sodium amytal, accurately weighed to constant weight at 90 C  
 0.5 Gm of sodium amytal  
 separatory funnel  
 10 cc of diluted sulfuric acid  
 10 cc of ether  
 extractions to dryness in a stream of warm air and dry to constant weight at 90 C. The amount of isoamylethylbarbituric acid corresponds to not less than 90 per cent nor more than 91 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible extraction to a tared platinum dish and evaporate to dryness on a steam bath to the residue obtained add 5 cc of sulfuric acid and heat cautiously until the excess of sulfuric acid has been volatilized, repeat twice using 1 cc of sulfuric acid each time add about 0.5 Gm of ammonium carbonate ignite to constant weight and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 8.9 per cent nor more than 9.5 per cent when calculated to the dried substance.

# LILLY LILLY AND COMPANY

## Sodium Amytal (Powder) 30 cc

U S patent 1,514,573 (Nov 4 1924 expired) U S trademark 161,125

Ampoules Sodium Amytal 0.065 Gm 0.125 Gm

Ampoules Sodium Amytal 0.25 Gm 0.5 Gm 1.0 Gm  
 Each ampule is accompanied by an ampule of distilled water

Pulvules Sodium Amytal 0.065 Gm and 0.130 Gm

Suppositories Sodium Amytal 0.130 Gm

## Formulary under Elixir Barbitals

*Actions and Uses*—See the preceding article Barbituric Acid Derivatives. Barbitals is quickly absorbed especially when it is given in solution. Small doses induce sleep apparently with little other effect and are relatively safe but fatalities have followed its indiscriminate use.

*Dosage*—As hypnotic 0.3 Gm best prescribed in the form of powder to be given in hot fluid such as hot milk half an hour or an hour before bedtime. Pills or tablets should be crushed before swallowing to insure absorption. From 0.1 to 0.15 Gm are used with analgetics for the relief of pain.

## ABBOTT LABORATORIES

Tablets Barbital: 0.3 Gm

## MALLINCKRODT CHEMICAL WORKS

Barbital (*Powder*): bulk.

## MERCK &amp; Co., INC.

Barbital (*Powder*): bulk.

Tablets Barbital: 0.3 Gm

## THE WM. S. MERRELL COMPANY

Tablets Barbital: 0.3 Gm.

## WINTHROP CHEMICAL COMPANY, INC.

Veronal (*Powder*): bulk.

U S patent 782,739 (Feb 14, 1905; expired). U S trademark 40,115

Tablets Veronal: 0.3 Gm

Elixir of Veronal: Each 4 cc. contains veronal 0.13 Gm in a menstruum containing alcohol 33.5 per cent.

**BARBITAL SODIUM.**—Soluble Barbital—Sodium Diethylbarbiturate.—Soluble Barbitone.—Sodium Diethylmalonylurea—U. S. P.—Medinal.—Veronal Sodium.— $C_8H_{12}O_4N_2Na$ .—M. W. 206.18—"Contains not less than 88 per cent and not more than 90 per cent of barbital ( $C_8H_{12}N_2O_4$ ), calculated on a moisture-free basis, the moisture being determined on a separate portion by drying at 100° C. for 3 hours." U. S. P.

For description and standards see the U. S. Pharmacopœia under Barbitalum Sodicum and Tabellae Barbitali Sodici

*Actions and Uses*.—The same as those of barbital. It is claimed, however, that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

*Dosage*.—The same as that of barbital. It should be administered in aqueous solution

## ABBOTT LABORATORIES

Tablets Barbital Sodium: 0.3 Gm

## MERCK &amp; Co., INC.

Barbital Sodium (*Powder*): bulk

Tablets Barbital Sodium: 0.3 Gm

## SCHIERING &amp; GLATZ, INC

Medinal (*Powder*): 40 cc bottles

U S. patents 780,241 (Jan 17, 1905, expired) and 829,499 (Feb 19 1908, expired) U S trademark 269,753

Elixir Medinal 200 cc and 384 liters. A solution containing in each 4 cc 0.12 Gm medinal in 20 per cent alcohol

Tablets Medinal 3 Gm

Suppositories Medinal 0.65 Gm

WINTHROP CHEMICAL COMPANY, INC.

Veronal Sodium (Powder) bulk

U. S. patent 787,739 (Feb. 14, 1905 exp. red.) U. S. trademark 40,115

Tablets Veronal Sodium 0.065 Gm

DIAL — 5,5-Diallylbarbituric acid — Diallylmalonylurea —  $C_8H_{12}O_5N$  — M. W. 208.21



*Actions and Uses*—The actions and uses of Dial are essentially similar to those of barbital but Dial is more active than barbital and it is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher centers of the brain and exert no injurious action on respiration or circulation. The hypnotic action is induced within from one half to one hour.

The actions and uses of Dial with urethane are the same as those of Dial. It is claimed that the ethyl carbamate and monoethylurea are used as solvents and in the amounts present do not greatly affect the action of the Dial content. Solution of Dial with urethane is proposed for intramuscular administration and in the case of a pressing emergency only for intravenous injection. The solution being strongly hypertonic subcutaneous injection should never be employed.

*Dosage*—As a sedative 0.03 Gm three or four times daily. As a hypnotic 0.1 to 0.3 Gm one half to one hour before sleep is desired.

#### *Tests and Standards*—

Dial occurs as a fine white crystalline powder with a slightly bitter taste, completely soluble in alcohol and ether, very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Dial melts at 117.3°C.

Place approximately 0.3 Gm Dial in a 25 cc glass stoppered cylinder add a mixture of 1 cc normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc of mercuric chloride solution, a white precipitate results, soluble in 10 cc of ammonia water. To the other portion add 5 cc of silver nitrate solution, a white precipitate results, soluble in 5 cc of ammonia water. Boil 0.5 Gm with 5 cc of a 25 per cent sodium hydroxide solution, it is decomposed with the evolution of ammonia. Dissolve 0.1 Gm in 1 cc of sulfuric acid, the liquid assumes a yellow color, changing slowly to a brown shred, finally to a dark red. Place 1 Gm. in a 25 cc glass stoppered cylinder add 10 cc of water, shake for one minute, filter through paper and divide into two portions. To one por-

tion add 0.5 cc. of a saturated bromine water; an immediate discoloration occurs; to the other portion add 0.1 cc. of tenth-normal potassium permanganate; a yellow color appears immediately.

Boil 0.5 Gm. of Dial with 50 cc. of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of Dial accurately weighed the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution, using thymolphthalein as an indicator; the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent, nor more than 101.5 per cent of diallylbarbituric acid.

#### CHIA PHARMACEUTICAL PRODUCTS, INC.

Dial (*Powder*): 10 Gm. and 120 Gm.

Tablets Dial: 0.03 Gm. and 0.1 Gm.

Elixir Dial: Each 4 cc. contains 0.05 Gm. in a menstruum containing alcohol 25 per cent.

Ampules Sterile Solution Dial with Urethane: 1 cc. and 2 cc. Each cubic centimeter contains Dial 0.1 Gm., ethyl carbamate (urethane) 0.4 Gm., monoethylurea 0.4 Gm. and water q. s.

U. S. patent 1,042,265 (Oct. 22 1912; expired) U. S. trademark 98,204 and 126,088

**EVIPAL SODIUM.**—Evipal Soluble—Sodium N-methylcyclohexenyl-methyl-barbiturate.—The sodium salt of 1,5-dimethyl-5- $\Delta^1$ -cyclohexenyl barbituric acid  $C_{11}H_{15}O_3N_2Na$ —M. W. 258.25



**Actions and Uses.**—The actions and uses of evipal sodium are essentially similar to those of pentobarbital sodium except that it is designed only for intravenous use to produce anesthesia of short duration. When injected intravenously it is a quick-acting, general anesthetic with an early recovery period. In the majority of cases, consciousness is restored in from fifteen to thirty minutes. The patient is not excited and is comfortable. Not uncommonly, the patient is left in a state of relaxation. biturates is a general anesthetic. It should be undertaken only by those experienced in this field. It should not be looked on as a routine office procedure; adequate facilities should be at hand to combat untoward reactions. Ataxia and transient amnesia may occasionally be encountered. Contraindications are in general those of the barbituric compounds and general anesthetics.

*Dosage*—As there is considerable variation in individual reactivity to any of the barbiturates the dose must be individualized. In general 2 cc to 4 cc of a 10 per cent solution is required to induce unconsciousness in adults, this is injected intravenously at the rate of 1 cc per ten seconds. An additional 1 cc or 2 cc may be necessary if relaxation is not obtained with the initial dose or it may be required during the operative procedure. A total amount of 10 cc of this 10 per cent solution is seldom required for adults, and it cannot be exceeded without danger.

*Caution*—If the solution is discolored or shows the presence of undissolved particles even though it is freshly prepared it should be discarded. The powder and solution undergo change on exposure to air and should not be kept for future use.

### Tests and Standards—

Evipal soluble occurs as a white crystalline odorless hygroscopic powder, with a slightly bitter taste, very soluble in water, freely soluble in alcohol, practically insoluble in ether. An aqueous solution of evipal soluble is alkaline to litmus.

Dissolve about 0.5 Gm of evipal soluble in 100 cc of water add an excess of diluted hydrochloric acid mix, allow to stand fifteen minutes and collect the resultant cyclohexenyldimethyl barbituric acid on a filter wash with water and dry at 65 C it melts at 143-146 C.

Transfer about 0.1 Gm of the dried cyclohexenyldimethyl barbituric acid to a stoppered cylinder add 25 cc of water shake the mixture for one minute filter through paper and divide into two portions, to one portion add 1 cc of acetic acid and 0.5 cc of water saturated with bromine an immediate discoloration occurs to the other portion add 0.1 cc of tenth normal potassium permanganate solution a pale brownish yellow color appears.

Transfer about 0.5 Gm of evipal soluble to a 50 cc Erlenmeyer flask

Boil about 0.5 Gm of evipal soluble with 5 cc. of a 25 per cent sodium hydroxide solution it is decomposed with evolution of ammonia.

Transfer about 0.3 Gm of evipal soluble to a test tube containing 2 cc of water and add dropwise a saturated solution of bromine in water until the

the test tube

filter through p

point of the pro

Incubate ab

metals)

Boil about 0.5 Gm of evipal soluble with 5 cc. of a 25 per cent sodium hydroxide solution it is decomposed with evolution of ammonia.

Dissolve about 0.5 Gm. of evipal soluble in 10 cc of water and divide the solution into two portions, to one portion add 1 cc of mercuric chloride solution a white precipitate results insoluble in excess water partially soluble in an excess of ammonia to the other portion add 5 cc of silver nitrate solution a white precipitate results soluble in excess water soluble in an excess of ammonia.

Dissolve about 0.5 Gm of evipal soluble in 50 cc of water add 5 cc of diluted nitric acid allow to stand for fifteen minutes and filter

through paper; separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*), no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*).

Add about 0.1 Gm. of evipal soluble to 2 cc. of sulfuric acid; the solution is pale yellow, gradually changing to brown-orange (*easily colorable substances*).

The pH of a 10 per cent solution of evipal soluble lies between 11 and 12. Dry about 1 Gm. of evipal soluble, accurately weighed, to constant weight at 65 C.; the loss in weight is negligible.

Transfer about 0.5 Gm., accurately weighed, of the dried evipal soluble to a tared porcelain dish, add 2 cc. of sulfuric acid, cautiously ignite until the excess of sulfuric acid has been volatilized, repeat the ignition twice with the addition of 1 cc. of sulfuric acid; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight and weigh as sodium sulfate; the percentage of sodium corresponds to not less than 8.5 nor more than 9.4 when calculated to the dried substance.

Transfer about 0.5 Gm. of evipal soluble, accurately weighed, to a suitable separator, add 15 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid; extract the mixture with eight successive portions of chloroform using 25 cc., 15 cc. and six portions of 10 cc., respectively, evaporate the combined chloroform extracts in a tared beaker to dryness in a stream of warm air and dry to constant weight at 65 C.; the amount of cyclohexenylmethyl barbituric acid corresponds to not less than 91 per cent nor more than 92 per cent, calculated to the dried substance.

Transfer about 0.25 Gm. of evipal soluble, which has been accurately weighed in a tared stoppered weighing bottle, to a glass stoppered Erlenmeyer flask with about 20 cc. of water. Add 50 cc. of tenth normal bromide-bromate solution and 10 cc. of hydrochloric acid, cool in ice with an occasional swirling for twenty minutes. Then add 10 cc. of 10 per cent potassium iodide solution (iodate free) and allow to stand for ten minutes. Titrate the free iodine with tenth normal sodium thiosulfate solution. When the titration is nearly complete, add 5 cc. of chloroform, using starch solution as the indicator, and continue the titration until colorless. Each cc. of tenth normal bromide-bromate solution is equivalent to 0.0129 Gm. of evipal soluble; the amount found corresponds to not less than 99 per cent nor more than 101 per cent.

### WINTHROP CHEMICAL COMPANY, INC.

**Ampules Evipal Soluble:** 0.5 Gm. and 1 Gm. powder packaged with or without sterile distilled water.

U. S. patent 1,947,944 U. S. trademark 315,515

**IPRAL CALCIUM.**—Calcium 5-ethyl-5-isopropylbarbiturate—The trihydrated calcium salt of 5-ethyl-5-isopropylmalonyl urea ( $C_8H_{15}O_3N_2$ ) $_2$ Ca  $3H_2O$ —M W 488.58

**Actions and Uses.**—Ipral calcium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours.

Ipral calcium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral calcium is not developed readily, but that its action is so persistent that a patient frequently sleeps on the night succeeding that when the hypnotic was administered.

**Dosage.**—From 0.12 to 0.25 Gm. followed by a cupful of hot water, tea or milk.

*Tests and Standards—*

Ipral calcium occurs as a white, crystalline, odorless powder with a slightly bitter taste. It is soluble in about 40 parts of water at 25 C, insoluble in alcohol. An aqueous solution is alkaline in reaction to litmus. Add 0.2 Gm to 20 cc of water, acidify with 5 cc. diluted hydrochloric acid, filter, make filtrate ammoniacal, then add 2 cc of ammonium oxalate solution; a precipitate forms, insoluble on addition of acetic acid in excess, but soluble on the addition of hydrochloric acid. Wash well the residue from the foregoing with water, dry at 100 C, the melting point should be from 200 to 203 C. To 0.05 Gm of residue add 2 cc sodium hydroxide solution; the residue dissolves. Place 2 Gm in a glass stoppered flask, treat with 25 cc of carbon dioxide free water and agitate occasionally over a period of two hours by decantation; separate the insoluble material, transfer the insoluble residue to a test tube, treat with diluted sulfuric acid and pass the emitted gases into 20 cc of barium hydroxide solution; not more than a barely perceptible turbidity should result (*limit of carbonate*). Dry about 1 Gm, accurately weighed, to constant weight at 100 C; the loss does not exceed 12 per cent. Transfer about 1 Gm, accurately weighed

to a 250 cc beaker, add 10 cc of water, stopper and shake the liquid through filter paper, transfer to a 250 cc beaker, add 10 cc of diluted hydrochloric acid, extract with five successive portions of ether, allow the solvent to evaporate spontaneously, dry the residue to constant weight at 100 C, and weigh; the weight of ethylisopropyl barbituric acid is not less than 78.5 per cent, nor more than 83.0 per cent. Ignite about 1 Gm, accurately weighed, cool, treat the residue with 5 cc diluted hydrochloric acid, transfer to a 250 cc beaker, add 25 cc water and ammonia water until ammoniacal, warm, add 20 cc boiling ammonium oxalate solution, boil and allow to stand overnight, collect the precipitate on an ashless filter paper, wash with diluted ammonia water (1 part of ammonia water to 5 parts of water), transfer the precipitate to a platinum crucible and ignite to constant weight; the weight of calcium oxide corresponds to not less than 8.0 per cent nor more than 8.5 per cent calcium.

**E. R. SQUIBB & SONS**

**Ipral Calcium (Powder):** 30 Gm bottle

U S patents 1,255,951 (Feb 12, 1918, expired), 1,576,014 (March 9, 1926, expires 1943) U S trademark 208,813

**Tablets Ipral Calcium:** 0.09 Gm and 0.12 Gm

**IPRAL SODIUM**—Sodium, 5 ethyl 5-isopropylbarbiturate  
—The sodium salt of 5 ethyl-5 isopropylmalonylurea— $C_{12}H_{17}N_2O_4Na$ —M W 220.21



**Actions and Uses**—Ipral sodium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours.

Ipral sodium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral sodium is not developed readily, and that its action is persistent.



through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*), no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*).

Add about 0.1 Gm. of *evipal soluble* to 2 cc. of sulfuric acid: the solution is pale yellow, gradually changing to brown-orange (*easily carbonizable substances*).

The pH of a 10 per cent solution of *evipal soluble* lies between 11 and 12. Dry about 1 Gm. of *evipal soluble*, accurately weighed, to constant weight at 65 C.: the loss in weight is negligible.

Transfer about 0.5 Gm., accurately weighed, of the dried *evipal soluble* to a tared porcelain dish, add 2 cc. of sulfuric acid, cautiously ignite until the excess of sulfuric acid has been volatilized, repeat the ignition twice with the addition of 1 cc. of sulfuric acid; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 8.5 nor more than 9.4 when calculated to the dried substance.

Transfer about 0.5 Gm. of *evipal soluble*, accurately weighed, to a suitable separator, add 15 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid; extract the mixture with eight successive portions of chloroform using 25 cc., 15 cc. and six portions of 10 cc., respectively, evaporate the combined chloroform extracts in a tared beaker to dryness in a stream of warm air and dry to constant weight at 65 C.: the amount of cyclohexenylidimethyl barbituric acid corresponds to not less than 91 per cent nor more than 92 per cent, calculated to the dried substance.

Transfer about 0.25 Gm. of *evipal soluble*, which has been accurately weighed in a tared stoppered weighing bottle, to a glass stoppered Erlenmeyer flask with about 20 cc. of water. Add 50 cc. of tenth normal bromide-bromate solution and 10 cc. of hydrochloric acid, cool in ice with an occasional swirling for twenty minutes. Then add 10 cc. of 10 per cent potassium iodide solution (iodate free) and allow to stand for ten minutes. Titrate the free iodine with tenth normal sodium thiosulfate solution. When the titration is nearly complete, add 5 cc. of chloroform, using starch solution as the indicator, and continue the titration until colorless. Each cc. of tenth-normal bromide-bromate solution is equivalent to 0.0129 Gm. of *evipal soluble*, the amount found corresponds to not less than 99 per cent nor more than 101 per cent.

#### WINTITROP CHEMICAL COMPANY, INC.

**Ampules Evipal Soluble; 0.5 Gm. and 1 Gm. powder** packaged with or without sterile distilled water

U S patent 1,947,944 U S trademark 315,515

**IPRAL CALCIUM.**—Calcium 5-ethyl-5-isopropylbarbiturate.—The trihydrated calcium salt of 5-ethyl-5-isopropylmalonyl urea ( $C_8H_{12}O_4N_2$ ),  $Ca_3H_3O$ —M W. 488.58

**Actions and Uses.**—Ipral calcium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours.

Ipral calcium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral calcium is not developed readily, but that its action is so persistent that a patient frequently sleeps on the night succeeding that when the hypnotic was administered.

**Dosage.**—From 0.12 to 0.25 Gm. followed by a cupful of hot water, tea or milk.

*Tests and Standards—*

Ipral calcium occurs as a white crystalline odorless powder with a slightly bitter taste. It is soluble in about 40 parts of water at 25 C insoluble in alcohol. An aqueous solution is alkaline in reaction to litmus. Add 0.2 Gm to 20 cc of water acidify with 5 cc diluted hydrochloric acid filter, make filtrate ammoniacal then add 2 cc of ammonium oxalate solution a precipitate forms insoluble on addition of acetic acid in excess but soluble on the addition of hydrochloric acid. Wash well the residue from the foregoing with water dry at 100 C the melting point should be from 200 to 203 C. To 0.05 Gm of residue add 2 cc sodium hydroxide solution the residue dissolves. Place 2 Gm in a glass stoppered flask treat with 25 cc of carbon dioxide free water and agitate occasionally over a period of two hours by decantation separate the insoluble material transfer the insoluble residue to a test tube treat with diluted sulfuric acid and pass the emitted gases into 20 cc of barium hydroxide solution not more than a barely perceptible turbidity should result (*limit of carbonate*). Dry about 1 Gm, accurately weighed to constant weight at 100 C the loss does not exceed 12 per cent. Transfer about 1 Gm accurately weighed to a glass stoppered cylinder add 50 cc of ether stopper and shake the contents for five minutes decant the supernatant liquid through filter paper and repeat using 25 cc. and 15 cc portions respectively of ether evaporate the filtrate to dryness in a tared beaker and dry to constant weight at 100 C the residue should not weigh more than 4 per cent (*limit of uncombined ethylisopropyl barbituric acid*). Dissolve about 1 Gm accurately weighed in water acidify with 10 cc of diluted hydrochloric acid extract with five successive portions of

not more than 8.5 per cent calcium

**E. R. SQUIBB & SONS**

Ipral Calcium (Powder) 30 Gm bottle

U S patents 1 255 931 (Feb 12 1918 expired) 1 576 014 (March 9 1926 expires 1943) U S trademark 208 813

Tablets Ipral Calcium 0.09 Gm and 0.12 Gm

**IPRAL SODIUM**—Sodium 5 ethyl 5 isopropylbarbiturate  
—The sodium salt of 5 ethyl 5 isopropylmalonylurea— $C_{12}H_{18}O_4Na$   
 $O_2N_2Na$ —M W 220.21



**Actions and Uses**—Ipral sodium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly but some action commonly persists for twenty four hours.

Ipral sodium is used as a hypnotic to combat restlessness irritability and sleeplessness. It is claimed that tolerance to ipral sodium is not developed readily and that its action is persistent.

**Dosage.**—From 0.12 to 0.25 Gm followed by a cupful of hot water, tea or milk.

**Tests and Standards.**—

**Caution:** Aqueous solutions of ipral sodium are not stable but decompose on standing; on boiling, a precipitation occurs.

Ipral sodium is a white hygroscopic powder, soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. An aqueous solution of ipral sodium has an alkaline reaction to litmus. Dissolve about 0.5 Gm. of ipral sodium in 100 cc of water, add an excess of diluted hydrochloric acid, collect the resultant ethylisopropyl barbituric acid on a filter, wash and dry at 100 C.; it melts at 200-205 C. Incinerate about 1 Gm. of ipral sodium, the residue responds to tests for sodium carbonate. Boil about 0.5 Gm of ipral sodium with 5 cc. of a 25 per cent sodium hydroxide solution; it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm of ipral sodium in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution; a white precipitate results, soluble in an excess of ammonia; to the other portion add 5 cc. of silver nitrate solution; a white precipitate results, soluble in an excess of ammonia.

Dissolve about 0.5 Gm. of ipral sodium in 50 cc of water, add 3 cc of diluted nitric acid and filter through paper; separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (chloride); no turbidity on the addition of 1 cc. of barium nitrate solution (sulfate). To about 0.2 Gm of ipral sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper, the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals). Add about 0.1 Gm. of ipral sodium to 1 cc of sulfuric acid; the solution is colorless (readily carbonizable substances).

Transfer about 1 Gm. of ipral sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc and 15 cc portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.; the residue does not exceed 0.2 per cent (uncombined ethylisopropyl barbituric acid).

Dry about 1 Gm. of ipral sodium, accurately weighed, to constant weight at 100 C.; the loss does not exceed 2 per cent. Transfer about 0.5 Gm. of ipral sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 100 C.; the amount of ethylisopropyl barbituric acid corresponds to not less than 88.5 per cent nor more than 90.5 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained, add 5 cc of sulfuric acid, heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc each of sulfuric acid each time; add about 0.5 Gm of ammonium carbonate, ignite to constant weight, and weigh as sodium sulfate the percentage of sodium corresponds to not less than 9.5 per cent nor more than 11.5 per cent when calculated to the dried substance.

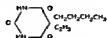
**E. R. SQUIBB & SONS**

**Elixir Ipral Sodium:** 13 Gm. in 1,000 cc.; 5 cc. is equivalent to 0.065 Gm of ipral sodium

**Tablets Ipral Sodium:** 0.25 Gm

U S patents 1,254,931 (Feb. 12, 1918, expired); and 1,576,014 (March 9 1926, expired) U S trademark 208,813

NEONAL—5 *n*-Butyl 5 ethylbarbituric acid — 5 *n* Butyl 5 ethylmalonylurea —  $C_{18}H_{24}O_4N_2$ —M W 212.24



**Actions and Uses**—The actions and uses of neonal are essentially similar to those of barbitol, but it is about three times as active as the latter, hence it is used in correspondingly smaller doses. It is claimed that it exerts a sedative action to an exceptional degree and that it is useful therefore in high nervous tension, neuroses and other conditions in which a sedative is required.

**Dosage**—From 0.05 to 0.4 Gm. For mild insomnias 0.05 to 0.1 Gm. is stated ordinarily to produce sleep. A dose of 0.4 Gm. is the maximum dose which should be required in the course of twenty-four hours administered in divided doses.

#### Tests and Standards—

Neonal occurs as a white crystalline odorless powder, with a slightly bitter taste, readily soluble in alcohol about 1 in 5 and ether about 1 in 10, very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 124-127° C. It is stable in air.

Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric chloride solution, a white precipitate results, soluble in 10 cc. of ammonia water. To the other portion add 5 cc. of silver nitrate solution, a white precipitate results, soluble in 5 cc. of ammonia water. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution. It is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid, the solution is colorless (readily carbonizable substances). Boil 0.5 Gm. with 50 cc. water for two minutes, no odor develops, cool and filter, separate portions of 10 cc. each of the filtrate, yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (chloride), no turbidity (sulfate), no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Incinerate about 1 Gm., accurately weighed, the residue does not exceed 0.1 per cent.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution, using thymolphthalein as an indicator. The amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of butylethylbarbituric acid.

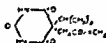
#### ABBOTT LABORATORIES

Neonal (Powder) • bulk

U. S. patent 1,609,520 (Dec. 7, 1926 expired) U. S. trademark 175,580

Tablets Neonol: 0.1 Gm.

**NOSTAL.**—5-Isopropyl-5-β-bromallyl barbituric acid—5-isopropyl-5-β-bromallyl malonylurea. —  $C_{15}H_{19}O_4N_3Br$ . — M. W. 289.14.



**Actions and Uses.**—The actions and uses of nostal are essentially similar to those of barbital, but nostal is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as an hypnotic.

**Dosage.**—As a sedative: 0.05 to 0.1 Gm. As an hypnotic: 0.1 to 0.3 Gm.; for children, 0.05 to 0.1 Gm according to age. Nostal should be administered preferably with a hot drink.

#### Tests and Standards.—

Nostal occurs as a colorless, crystalline, odorless powder, with a slightly bitter taste; readily soluble in alcohol, glacial acetic acid and acetone; sparingly soluble in ether, chloroform, benzene and water. A saturated aqueous solution is acid to litmus paper. Nostal melts at 177-179 C.

Fuse about 0.1 Gm. of nostal and 1 Gm. of crushed potassium hydroxide previously moistened with 1 cc. of alcohol in a nickel crucible. It is decomposed with the evolution of ammonia; cool, dissolve the residue in 10 cc. of water, add 10 cc. of diluted nitric acid, filter through paper, to the filtrate add 5 cc. of silver nitrate solution; a curdy, dirty white precipitate results, soluble in a large excess of stronger ammonia water. Place approximately 0.3 Gm. of nostal in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution; a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution; a white precipitate results, soluble in 5 cc. of ammonia water.

Boil about 0.5 Gm. of nostal with 50 cc. of water for two minutes; no odor develops, cool and filter, separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (soluble halides); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (sulfate), no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Incinerate about 1 Gm. of nostal, accurately weighed; the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution. The amount of tenth normal sodium hydroxide solution required is to not less than 27.5 per cent.

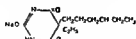
RIEDEL-DE-HAEN, INC.

**Nostal (Powder):** bulk.

U. S. patent 1,622,129 (March 22, 1927; expires 1944). U. S. trade mark 270,750.

**Tablets Nostal:** 0.1 Gm.

**ORTAL-SODIUM**—Sodium 5 *n*-hexyl 5-ethyl barbiturate—Sodium *n* hexylethyl malonylurea—The monosodium salt of 5-*n* hexyl 5 ethyl barbituric acid— $C_{12}H_{19}O_3N_2Na$ —M W 262.29



**Actions and Uses**—The actions and uses of ortal sodium are essentially similar to those of barbital, but ortal sodium is more active than barbital and it is used in correspondingly smaller doses

**Dosage**—From 0.2 to 0.4 Gm followed by a glass of water. It is rarely necessary to give more than 1 Gm in twenty four hours. When oral administration is contraindicated, ortal sodium may be administered rectally.

**Caution** Aqueous solutions of ortal sodium are not stable but decompose on standing, on boiling a precipitation occurs with evolution of ammonia.

#### Tests and Standards—

Ortal-sodium is an odorless white or slightly yellowish powder with a bitter taste, very soluble in water, soluble in alcohol, practically insoluble in ether and benzene. An aqueous solution of ortal sodium has an alkaline reaction to litmus.

Dissolve about 0.5 Gm of ortal sodium in 100 cc of water, add an excess of diluted hydrochloric acid, collect the resultant hexylethyl

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Transfer about 1 Gm of ortal sodium accurately weighed to a glass stoppered cylinder add 50 cc of anhydrous ether stopper and shake for ten minutes decant the supernatant liquid through filter paper and repeat twice using 25 cc and 15 cc portions, respectively of ether utilizing the same filter, evaporate the combined filtrates to dryness

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a stream of warm air and dry to constant weight at 90 C the amount of hexyl barbituric acid corresponds to not less than 99.8 per cent

nor more than 91.6 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 85 per cent, nor more than 9 per cent when calculated to the dried substance.

## PARKE, DAVIS & COMPANY

**Capsules Ortol Sodium:** 0.05 Gm., 0.2 Gm., 0.3 Gm.

U. S. patent 1,624,546 (April 12, 1927; expired 1944) U. S. trade mark 302,616.

**PENTOBARBITAL SODIUM.**—Soluble Pentobarbital "Contains not less than 90 per cent and not more than 92 per cent of pentobarbital ( $C_{11}H_{11}N_2O_3$ ), calculated on a moisture-free basis, the moisture being determined on a separate portion by drying at 90° C. for six hours." U. S. P.

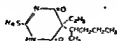
For description and standards see the U. S. Pharmacopeia under Pentobarbitalum Sodicum, Capsulae Pentobarbitali Sodici and Tabellae Pentobarbitali Sodici.

**Actions and Uses.**—The actions and uses of pentobarbital sodium are essentially similar to those of barbitol, but it is effective in smaller doses. It may be administered by mouth and rectum and may be injected intravenously (see general article on barbituric acid derivatives). The action is of relatively brief duration, which may constitute an advantage, especially when relatively large doses are administered. It is used as a sedative, particularly prior to local, general or spinal anesthesia. It can be used safely for such purposes only by those who have had adequate experience and who are familiar with the literature concerning such use.

**Dosage.**—Orally, as hypnotic, 0.1 Gm.; as preanesthetic sedative, 0.2 Gm. Rectally, for analgesia: for infants up to 1 year, 0.03 Gm., up to 3 years, 0.06 Gm.; for adults, 0.32 to 0.38 Gm. dissolved in a few cubic centimeters of water. Average intravenous dose for adults has been 0.2 to 0.3 Gm.; for children has not been definitely decided, although a child 6 to 12 years may receive up to 0.1 to 0.2 Gm.

**Caution:** Aqueous solutions of pentobarbital sodium are not stable but decompose on standing; on boiling, a precipitation occurs with evolution of ammonia.

**PENTOTHAL SODIUM.**—Sodium 5-ethyl-5-(1-methylbutyl) thiobarbiturate. The monosodium salt of 5-ethyl-5-(1-methylbutyl) thiobarbituric acid —  $C_{14}H_{19}O_2N_2SNa$  — M. W. 264.32



*Actions and Uses*—The actions and uses of pentothal sodium are essentially similar to those of pentobarbital sodium except

pentothal sodium is not recommended in major operative procedures requiring long anesthesia or for office procedures. It should be employed only by competent, experienced anesthetists or surgeons who have at their hands facilities to combat problems involving respiratory depression and carbon dioxide-oxygen balance.

*Dosage*—Two or three cc of a 5 per cent solution is injected in about ten or fifteen seconds. The injection is then stopped to permit the complete effect to appear, which requires from thirty to thirty-five seconds. If relaxation has not occurred an additional 2 or 3 cc may be injected at the same rate as before.

*Caution* Aqueous solutions of pentothal sodium are not stable but decompose on standing, on boiling, a precipitation occurs.

#### *Tests and Standards*—

Pentothal sodium occurs as a yellowish white hygroscopic powder, possessing a sulfur like odor, soluble in water and alcohol, insoluble in

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sodium the residue responds to tests for sodium carbonate and very faintly for sulfide. Boil about 0.2 Gm of pentothal sodium with 25 per cent sodium hydroxide solution, no evolution of ammonia occurs. Dissolve about 0.1 Gm of pentothal sodium in 10 cc of water, add 1 cc of mercuric chloride a white precipitate results, soluble in an excess of ammonia.

Dissolve about 0.5 Gm of pentothal sodium in 50 cc of water, add 5 cc of diluted nitric acid and filter through paper. Separate portions of 10 cc each of the filtrate yield a faint opalescence on the addition of 1 cc of silver nitrate solution (*chloride*), very slight turbidity on the addition of 1 cc barium nitrate solution (*sulfate*). To about 0.2 Gm of pentothal sodium in 25 cc of water add 1 cc of diluted hydrochloric acid, filter through paper. The filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

dried substance

Transfer the acidulated aqueous portions from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on



a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 85 per cent nor more than 88 per cent when calculated to the dried substance.

#### *Pentothal sodium with anhydrous sodium carbonate*

Dissolve about 0.5 Gm. of pentothal sodium with anhydrous sodium carbonate in 100 cc. of water; add an excess of diluted hydrochloric acid; collect the resultant ethyl (1-methylbutyl) thiobarbituric acid on a filter paper, wash and dry at 70 C.; it melts at 156-159 C. Boil about 0.2 Gm. of pentothal sodium with anhydrous sodium carbonate with 25 per cent sodium hydroxide solution; no evolution of ammonia occurs.

Dissolve about 0.5 Gm. of pentothal sodium with anhydrous sodium carbonate in 50 cc. of water; add 5 cc. of diluted nitric acid and filter through paper; separate portions of 10 cc. each of the filtrate yield a faint opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); very slight turbidity on the addition of 1 cc. barium nitrate solution (*sulfate*). To about 0.2 Gm. of pentothal sodium with anhydrous sodium carbonate in 25 cc. of water add 1 cc. of diluted hydrochloric acid, filter through paper; the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm. of pentothal sodium with anhydrous sodium carbonate, accurately weighed, at 70 C., for twenty-four hours; the loss in weight should not exceed 2 per cent.

Transfer about 0.3 Gm. of pentothal sodium with anhydrous sodium carbonate, accurately weighed, to a suitable Squibb separatory funnel; add 50 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid; extract with six successive portions of chloroform using 25 cc., 25 cc., 20 cc., 15 cc., 15 cc. and 10 cc., respectively, evaporate the combined chloroformic extractions to dryness in a stream of warm air and dry to constant weight at 70 C.; the percentage of ethyl (1-methylpropyl carbonyl) thiobarbituric acid should correspond to not less than 84 per cent nor more than 87 per cent when calculated to the dried substance.

Transfer the acidulated aqueous portions from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using 1 cc. portions of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 100 per cent nor more than 107 per cent when calculated to the dried substance.

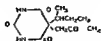
#### ABBOTT LABORATORIES

**Ampoules Pentothal Sodium:** 0.5 Gm. and 1.0 Gm. with 0.03 Gm. and 0.06 Gm. anhydrous sodium carbonate respectively, as buffer.

**Ampoules Pentothal Sodium:** 50 Gm. with 0.3 Gm. anhydrous sodium carbonate as a buffer. Multiple dose ampul

U. S. patent 2,153,720 (April 11, 1939, expires 1956). U S trade mark 334,340

**PERNOSTON.**—5-sec Butyl-5-β-bromallyl barbituric acid—5-(butyl-2)-5 β-brompropenyl malonylurea— $C_{11}H_{11}O_5N_2Br$ —M W 303.16



**Actions and Uses.**—The actions and uses of pernoston are essentially similar to those of barbital, but pernoston is more active than barbital and is used in correspondingly smaller doses. It is promptly absorbed and is rapidly changed and destroyed within the body. It is used in combating insomnia due to emotional strain and nervous instability.

**Dosage.**—One tablet (194 mg) given one-half hour before sleep is desired, preferably followed by a glass of warm milk or lemonade. For hypnosis in the presence of pain one tablet given in conjunction with acetylsalicylic acid.

### Tests and Standards—

Pernoston occurs as a fine, white, crystalline powder with a slightly bitter taste, completely soluble in alcohol and ether, very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Pernoston melts at 130 to 133 C.

Place approximately 1 Gm of pernoston in a 25 cc glass stoppered cylinder, shake for 1 minute, add 5 cc of silver nitrate solution, a white precipitate results, soluble in 5 cc of ammonia water.

Fuse about 0.1 Gm of pernoston and 1 Gm of crushed potassium hydroxide, previously moistened with 1 cc of alcoholic potassium hydroxide solution in a nickel crucible; it is decomposed with the evolution of ammonia, cool, dissolve the residue in 10 cc of water, add 10 cc of diluted nitric acid, filter through paper, to the filtrate add 5 cc of silver nitrate solution, a curdy dirty white precipitate results, soluble in excess of stronger ammonia water.

Dissolve 0.1 Gm of pernoston in 1 cc of sulfuric acid, the liquid assumes a yellow color, changing slowly to a brownish red, finally to a dark red. Place 1 Gm of pernoston in a 25 cc glass stoppered cylinder, add 10 cc of water, shake for one minute, filter through paper and divide into two portions, to one portion add 0.5 cc of a saturated bromine water, an immediate discoloration occurs, to the other portion add 0.1 cc of tenth normal potassium permanganate, a yellow color appears immediately.

Boil 0.5 Gm of pernoston with 50 cc of water for two minutes, no odor develops, cool and filter, separate portions of 10 cc each of the

Incinerate about 1 Gm of pernoston, accurately weighed, the residue does not exceed 0.1 per cent. Transfer about 0.25 Gm of pernoston, accurately weighed, to a bomb tube; determine the bromine content by the Carius method, the amount of bromine found should be not less than 26.1 per cent nor more than 26.6 per cent. Dissolve about 0.5 Gm of pernoston, accurately weighed, in 25 cc of previously neu

tralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator; the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of *sec.* butyl bromallyl barbituric acid.

RIEDEL-DE HAEN, INC.

**Pernoston (Powder):** bulk.

U. S. patent 1,739,662 (Dec. 17, 1929; expires 1946). U. S. trade mark 266,216.

Tablets Pernoston: 194 mg.

**PERNOSTON SODIUM.**—Sodium 5-*sec.* butyl-5- $\beta$ -bromallylbarbiturate. — Sodium 5-(butyl-2)-5- $\beta$ -bromopropenylmaloylurea. The sodium salt of pernoston— $C_{21}H_{21}O_4N_2Br.Na$ —M. W. 325.15.

**Actions and Uses.**—The action of pernoston sodium is like that of pernoston except that the effects are induced almost immediately after its intravenous injection. It is used when the oral administration of a barbiturate is not feasible either because of interference with swallowing and when prompt action is imperative, as in the presence of convulsions. The effects are delayed for from thirty to forty-five minutes after the intramuscular injection. The intravenous use demands the rigid observance of the proper technic. The contraindications are important.

**Dosage.**—One cc. of the 10 per cent solution (in ampuls) per 12.5 Kg. of body weight injected intravenously at the rate of 1 cc. total per minute until the patient sleeps or until the full dose has been injected. The intramuscular dose is the same as that by vein, but it may be injected at once. Ampules containing a deposit should not be used.

**Tests and Standards.**—

Pernoston sodium occurs as a fine, white, crystalline powder, possessing a bitter taste; soluble in water and alcohol, slightly soluble in ether and chloroform. A 10 per cent aqueous solution is alkaline to litmus and phenolphthalein and has a *pH* of approximately 9.5.

Transfer 5 cc. of a 10 per cent solution of pernoston sodium to a test tube, add 2 cc. of diluted hydrochloric acid; allow the precipitate to crystallize, filter, wash and recrystallize from an ethanol-water mixture. the melting point of the pernoston is from 130 to 133 C.

Transfer 5 cc. portions of a 10 per cent solution of pernoston sodium to two test tubes and to one add 1 cc. of mercury bichloride solution; a white precipitate results, soluble in 10 cc. of ammonium hydroxide; to the other portion add 5 cc. of silver nitrate solution; a white precipitate results, soluble in 5 cc. of ammonium hydroxide.

Dissolve 0.1 Gm. of pernoston sodium in 1 cc. of sulfuric acid; the liquid assumes a yellow color, changing to brownish red and finally to dark red. Acidify 40 cc. of a 10 per cent solution of pernoston sodium with diluted nitric acid and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Transfer about 0.5 Gm of pernoston sodium previously dried and accurately weighed to a tared porcelain dish and add 2 cc of sulfuric acid, evaporate the excess acid ash the residue and ignite at 900 C the weight of sodium sulfate is not less than 21.4 per cent nor more than 22.2 per cent. Transfer about 0.3 Gm of pernoston sodium dried and accurately weighed to a bomb tube and determine the bromine content by means of the Carius method the bromine found is not less than 24.3 per cent nor more than 24.8 per cent. Transfer a sample of pernoston sodium dried and accurately weighed to a kjeldahl flask and digest with sulfuric acid in the presence of selenium dilute make alkaline distil into standard acid and titrate the excess acid with standard alkali the nitrogen content is not less than 8.3 per cent nor more than 8.8 per cent.

### RIFDEL DE HAEN, INC

**Ampules Solution Pernoston Sodium, 10%, 2 cc**

U S patent 1739 662 (Dec 17, 1929 expires 1946) U S trade mark 330 845

**PHANODORN**—Cyclobarbitol—Cyclohexenyl ethyl barbituric acid— $5\Delta^1$  cyclohexenyl 5 ethyl malonylurea— $C_{21}H_{24}O_4N_2$ —M W 236.26



**Actions and Uses**—The actions and uses of phanodorn resemble those of barbitol. It is eliminated more rapidly than barbitol, hence the action is not so lasting. This is an advantage when it is used merely to put one to sleep and sleep will then continue without its further action. It is used mainly for its sedative action in neurasthenia, psychoses and various types of insomnia.

**Dosage**—For the mildest type of simple insomnia, 0.1 Gm or  $\frac{1}{2}$  tablet. In intractable or obstinate insomnia, from 0.2 to 0.4 Gm or one to two tablets. The larger dose should not be repeated within less than twelve hours. The average dose is 0.2 Gm or one tablet.

### Tests and Standards—

Phanodorn occurs as a white crystalline odorless powder with a bitter taste, readily soluble in alcohol about 1 in 5 and ether, about 1 in 10, very slightly soluble in benzene and cold water. A saturated aqueous solution is acid to litmus paper. It melts at 171-174 C.

Dissolve 0.1 Gm in 1 cc of sulfuric acid the liquid assumes a yellow color changing quickly to orange and finally to red. Place 0.3 Gm in a 25 cc graduated cylinder, add 10 cc of water, 1 cc of sodium hydroxide solution and filter through paper. A white precipitate will form.

5 cc. of ammonia water will dissolve the precipitate. Boil 0.5 Gm. with 5 cc. of a 20 per cent sodium hydroxide solution. It is decomposed with the evolution of ammonia.

Boil 0.5 Gm with 50 cc of water for two minutes; no odor develops and filter; separate portions of 10 cc each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (chloride); no turbidity with 1 cc of diluted nitric acid and

1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm accurately weighed, there is not more than 0.01 per cent residue.

Dissolve about 0.5 Gm, accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution, using thymolphthalein as an indicator; the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent.

#### WINTHROP CHEMICAL COMPANY, INC.

Tablets Phenodorn: 194 mg.

U. S. patent 1,690,796 (Nov. 6, 1928; expires 1945).

**PHENOBARBITAL.**—Phenylethylmalonylurea.—Phenobarbitone.—U. S. P.—Luminal.

For description and standards see the U. S. Pharmacopeia under Phenobarbitalum, Tabellae Phenobarbitali, and Elixir Phenobarbitali.

*Actions and Uses*—The introduction of the phenyl group increases the hypnotic and sedative action of phenobarbital over that of barbital. The toxicity appears to be increased in about the same ratio. The sleep may be preceded by a period of excitement. Moderately large therapeutic doses sometimes cause severe circulatory depression. The formation of a habit has been reported.

Phenobarbital has a sedative action on respiration, lessening the frequency of breathing. It is eliminated by the kidneys, a certain portion being probably decomposed in the organism. No gastric disturbances have been observed.

Phenobarbital is used as a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system; its chief use in this field is as a sedative, and as an antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. Its use as a sedative has also been proposed in chorea, neurasthenia, cardiac and gastric neuroses, climacteric disorders, dysmenorrhea, exophthalmic goiter, and preoperative and postoperative cases.

*Dosage.*—From 0.015 to 0.2 Gm. increased if necessary to 0.6 Gm. The average dose is 0.1 Gm. A maximum dose of 0.6 Gm should not be exceeded.

#### ABBOTT LABORATORIES

Phenobarbital (*Powder*): bulk

Tablets Phenobarbital: 16 mg., 32.5 mg., 0.1 Gm.

#### AMERICAN PHARMACEUTICAL CO., INC.

Tablets Phenobarbital: 0.032 Gm., 0.016 Gm. and 0.1 Gm.

#### GEORGE A. BREON & COMPANY, INC.

Tablets Phenobarbital: 32.4 mg. and 109 mg.

## FLINT, EATON &amp; COMPANY

Tablets Phenobarbital (White and Green) 0.016 Gm  
0.032 Gm and 0.1 Gm

## GANE &amp; INGRAM, INC

Phenobarbital (*Powder*) bulk

## MERCK &amp; Co., INC

Phenobarbital (*Powder*) bulk

## THE WM S MERRELL COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 0.1 Gm

## THE SMITH DORSEY COMPANY

Tablets Phenobarbital 8 mg 16 mg 32.5 mg and 0.1 Gm

## THE UPJOHN COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 0.1 Gm Supplied in both white and green tablets

## THE WARREN FEEB PRODUCTS CO

Tablets Phenobarbital 16 mg 32.5 mg 0.1 Gm

## WINTHROP CHEMICAL COMPANY, INC

Luminal (*Powder*) bulk

U S patent 1,075,872 (May 7 1912 expired) U S trademark 87,327

Elixir of Luminal Each 4 cc contains 0.0162 Gm in a menstruum containing alcohol 26 per cent

Tablets Luminal 162 mg 324 mg and 109 mg

**PHENOBARBITAL SODIUM**—Soluble Phenobarbital Soluble Phenobarbitone—U S P—Luminal Sodium—"Contains not less than 89 per cent and not more than 91.5 per cent of phenobarbital ( $C_{12}H_{11}N_2O_3$ ) calculated on a moisture free basis the moisture being determined on a separate portion by drying at 140° C for 6 hours U S P

For description and standards see the U S Pharmacopeia under Phenobarbitalum Sodium and Tabellae Phenobarbitali Sodici

*Actions and Uses*—The same as those of phenobarbital except that it may be injected

*Dosage*—For hypodermic injection phenobarbital sodium is used in the form of 20 per cent solution prepared by dissolving the salt in boiled and cooled distilled water 2 cc of the solution contains 0.4 Gm of phenobarbital sodium

Phenobarbital sodium may be given hypodermically in doses of 0.1 to 0.3 Gm

*Caution* Aqueous solutions of phenobarbital sodium are not stable but decompose on standing on boiling a precipitation occurs

## ARBOTT LABORATORIES

Phenobarbital Sodium (*Powder*): bulk.

Ampoules Phenobarbital Sodium (*Powder*): 0.13 Gm

Tablets Phenobarbital Sodium, Hypodermic: 0.065 Gm

Tablets Phenobarbital Sodium: 0.1 Gm.

## ENDO PRODUCTS, INC.

Ampuls Sodium Phenobarbital Solution in Propylene Glycol: 2 cc. Each cubic centimeter contains phenobarbital sodium 0.16 Gm, dissolved in propylene glycol.

Sodium Phenobarbital Solution in Propylene Glycol: 0.325 Gm, in 2 cc. ampuls.

## GANE &amp; INGRAM, INC.

Phenobarbital Sodium (*Powder*): 30 cc., 60 cc. and 120 cc. bottles.

Tablets Phenobarbital Sodium: 109 mg.

## THE LAKESIDE LABORATORIES, INC.

Ampules Phenobarbital Sodium (*Powder*): 0.13 Gm

Ampuls Solution Phenobarbital Sodium and Benzyl Alcohol: 1 cc. and 2 cc. Each cubic centimeter contains 0.162 Gm. of phenobarbital sodium and 0.02 Gm. of benzyl alcohol dissolved in propylene glycol.

## MAILINCKRODT CHEMICAL WORKS

Phenobarbital Sodium (*Powder*): bulk.

## MERCK &amp; CO., INC.

Phenobarbital Sodium (*Powder*): bulk

## WINTHIROP CHEMICAL COMPANY, INC.

Luminal Sodium (*Powder*): bulk.

U. S. patent 1,025,872 (May 7, 1912; expired) U. S. trademark 87,327.

Ampules Luminal Sodium Solution in Propylene Glycol: 2 cc. Each cubic centimeter contains luminal sodium 0.16 Gm, dissolved in propylene glycol. The solution may be administered intramuscularly or subcutaneously but not intravenously.

Ampules Luminal-Sodium (*Powder*): 130 mg. and 324 mg.

Tablets Luminal-Sodium: 162 mg., 324 mg and 109 mg

Tablets Luminal-Sodium, Hypodermic: 648 mg.

**SANDOPTAL**—5 is 1 nyl 5 allyl 1 trichloro acid—5 is 1  
1 nyl 5 allyl 1 nyl nylurea— $C_8H_{10}O_2N_2$ —M. W. 224.25



**Actions and Uses**—The same as those of barbital and its therapeutically useful derivatives.

**Dosage**—1 or milligrams min. 0.2 Gm. for use in chronic cases of insomnia 0.4 to 0.8 Gm.

#### Tests and Similarity—

Sandoptal occurs as a white crystalline odorless powder with a slightly bitter taste, completely soluble in ethyl alcohol, acetone, chloroform, ether, ethyl acetate and glacial acetic acid, slightly soluble in cold water, sparingly soluble in boiling water and petroleum ether, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 138-139°C. It is stable in air.

Place about 0.3 Gm. of sandoptal in a 25 cc. glass stoppered cylinder add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions, to one portion add 1 cc. of mercuric chloride solution, a white precipitate results, soluble in 10 cc. of ammoniacal water, to the other portion add 5 cc. of silver nitrate solution, a white precipitate results, soluble in 5 cc. of ammoniacal water. Dissolve about 0.5 Gm. of sandoptal with 5 cc. of a 25 per cent sodium hydroxide solution, it is decomposed with the evolution of strongly alkaline vapors. Place about 1 Gm. of sandoptal in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions, to one portion add 1 cc. of acetic acid and 0.5 of a saturated bromine water, an immediate discoloration occurs, to the other portion add 0.1 cc. of tenth normal potassium permanganate solution, a yellow color appears immediately, turning to brown.

Dissolve about 0.1 Gm. of sandoptal in 1 cc. of sulfuric acid, the solution is colorless (*readily carbonizable substances*). Boil about 0.5 Gm. of sandoptal with 50 cc. of water for two minutes, no odor develops, cool and filter, separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*), no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*), no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of sandoptal, accurately weighed, the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm. of sandoptal, accurately weighed, in 25 cc. of previously neutralized alcohol dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator, the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isobutyl allyl barbital.

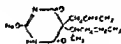
SANDOZ CHEMICAL WORKS, INC.

Tablets Sandoptal 0.2 Gm.

U. S. Trademark applied for



**SECONAL SODIUM.**—Sodium 5-allyl-5-(1-methylbutyl)barbiturate.— $C_{11}H_{19}O_3N_2Na$ .—M. W. 260.27.



**Actions and Uses.**—The actions and uses of seconal sodium are essentially those of barbital but it is described as a short-acting barbiturate. It is more active than barbital and is used in correspondingly smaller doses.

**Dosage.**—The average adult dose is from 0.1 to 0.2 Gm. When oral administration is contraindicated, seconal sodium may be administered rectally. Smaller doses of seconal sodium are sedative, larger doses are hypnotic. For use in obstetrics and as a preanesthetic sedative the following dosage has been suggested: In obstetrics, an initial dose of 0.3 Gm. followed by 0.7 Gm. to 0.2 Gm. doses at appropriate intervals up to a total of no more than 1.2 Gm. within a twelve hour period. as a preanesthetic agent, 0.2 Gm. to 0.3 Gm. one-half to one hour before the patient is sent to the operating room.

#### Tests and Standards.—

Seconal sodium occurs as a white, hygroscopic, odorless powder, possessing a bitter taste; very soluble in water, soluble in alcohol and practically insoluble in ether. An aqueous solution of seconal sodium is alkaline to litmus.

Dissolve about 1 Gm. of seconal sodium in 100 cc. of distilled water in a 500 cc. beaker and add sufficient 1 per cent acetic acid to make the solution distinctly acid to litmus. Stir vigorously for a few minutes and add an additional 150 cc. of distilled water. Heat to boiling and boil until the precipitate dissolves and no oily particles float on the surface of the liquid. Allow the solution to stand overnight at room temperature. Collect the resultant crystals of allyl (1-methyl butyl) barbituric acid on a porous plate and dry at room temperature; the crystals melt between 96 and 100 C. Dissolve 0.1 Gm. of seconal sodium in 10 cc. of distilled water and divide the solution into two portions; to one portion add 1 cc. of mercuric chloride solution; a white precipitate results, soluble in excess of ammonia water; to the other portion add 5 cc. of silver nitrate solution; a white precipitate results, soluble in excess of ammonia water. Transfer about 0.5 Gm. of seconal sodium to a 50 cc. beaker and boil with 5 cc. of a 25 per cent solution of sodium hydroxide; the product decomposes and ammonia is evolved. Dissolve about 0.5 Gm. of seconal sodium in 50 cc. of distilled water, add 5 cc. of diluted nitric acid and filter through paper. Separate 10 cc. portions of the filtrate yield no turbidity on the addition of 1 cc. of barium chloride solution (sulfate) and no more opalescence on the addition of 1 cc. of silver nitrate solution than is produced by 0.5 cc. of fiftieth normal hydrochloric acid in 50 cc. of distilled water (chloride). To about 0.2 Gm. of seconal sodium and 25 cc. of water add 1 cc. of diluted hydrochloric acid and filter through paper; the filtrate yields no coloration or precipitate when saturated with hydrogen sulfide (heavy metals). A solution prepared by dissolving 0.5 Gm. of seconal sodium in 5 cc. of sulfuric acid develops no more color after five minutes standing than matching fluid II described in the U.S.U. XI under the tests for carbonizable impurities. Dissolve about 1 Gm. of seconal sodium in 10 cc. of water and add one drop of a 5 per cent solution of potassium permanganate; the purple color is discharged and a brown

than in those of the petit mal. It does not cure congenital mental defects or the mental deterioration often observed in the epileptic. Various side actions of different degrees of severity which have been observed include dizziness, dry skin, dermatitis, rash, itching, tremors, fever, nausea, vomiting, blurred vision, fatigue, apathy, difficult breathing and swallowing, nervousness, mental confusion and active hallucinations, and hyperplasia of the gums suggestive of scurvy, though its use does not interfere with the utilization of vitamin C. Diphenylhydantoin sodium is strongly alkaline and it may give rise to gastric irritation.

**Dosage**—The optimum dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects by the physician. The influence of the drug on seizures and the appearance of any of the side actions enumerated must be a guide to the dosage. Mild symptoms do not necessarily require that the dosage be stopped. The beginning adult dose is 0.1 Gm (1½ grains) with at least half a glass of water three times daily

and to prevent gastric irritation) twice a day. Obviously such doses require the most careful supervision. If this dose is borne without side actions the dosage may be increased to 0.03 Gm (one half grain) three or four times a day. Every slight increase in dosage is made only after the physician is convinced that such increase is necessary and that no harm is to be anticipated.

The transition from phenobarbital, bromides or other hypnotic type drugs to diphenylhydantoin sodium should be made gradually with some overlapping in dosage. By this procedure the danger of phenobarbital or bromide withdrawal symptoms (increased number of seizures) is minimized and side actions incident to the beginning administration of diphenylhydantoin sodium are lessened.

**PARKE, DAVIS & COMPANY**

**Kapseals Dilantin Sodium 0.1 Gm and 0.03 Gm \***

U. S. trademark applied for

## CHAPTER XXI

### SERUMS AND VACCINES

Under this heading are described in the following pages agents of a complex biologic nature which are used in diagnosis, in prevention, and in the treatment of disease and which depend for their action on various phases and relations of immunity.

*Federal Regulations.*—The urgent need for control of many of these potent and, in some cases, dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes." Under this law the importation, exportation or interstate sale of these products is expressly forbidden unless the manufacturer holds a license issued on the recommendation of the U. S. Public Health Service.

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are imported or shipped for exportation or interstate sale. Only products which are licensed under the law referred to and which have not been found to conflict with the rules of the Council will be found listed here. In purchasing the products for use, preference should be given to those which have been kept continually at a low temperature.

*Dating of Biologic Products.*—The federal law requires that each package of biologic products be marked with an expiration date, "the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific result." The regulations framed under this law, as outlined below, prescribe for each class of product how long after date of manufacture or issue this expiration date may be; but the temperature at which the product is kept after leaving the manufacturer's hands cannot be controlled. Physicians would do well to secure their biologic products from stocks which are shown by actual continuous thermometer records to have been kept in cold storage. This is particularly applicable to the more rapidly deteriorating products, such as smallpox vaccine and the various immune serums.

Official potency standards have been established, or official potency tests are made at the National Institute of Health prior to the release of each lot, for the following products: botulinus antitoxin, diphtheria antitoxin, *Cl histolyticum* antitoxin, *Cl oedematiens* antitoxin, staphylococcus antitoxin, tetanus antitoxin, scarlet fever streptococcus antitoxin, perfringens antitoxin, vibron septique antitoxin, diphtheria toxin-antitoxin mixture, diphtheria toxoids, tetanus toxoids, antidysenteric serum, anti-meningococcic serum, type specific antipneumococcic serum, bacterial vaccines prepared from paratyphoid bacillus A, paratyphoid bacillus B, and typhoid bacillus, diphtheria toxin for the

Schick test and scarlet fever streptococcus toxin for the Dick test and for immunization. For these products the dating of each lot is based on the last test for potency, that is, the date of manufacture is taken as the last date of satisfactorily passing a potency test. For all other biologic products, the testing for potency is on a less satisfactory basis, and the date of manufacture is counted as the date of removal from the animal in case of animal products, or the date of cessation of growth in the case of other products. For the purpose of determining the expiration date, the date of issue may be used instead of the date of manufacture, provided the product has been kept between the date of manufacture and the date of issue not longer than the following periods, at the corresponding temperature: twenty-four months constantly below 0 C, or twelve months constantly below 5 C, or six months constantly below 10 C, or three months constantly below 15 C.

*Added Preservatives*—The safeguarding of serums, vaccines etc., against bacterial contamination usually requires the addition of some antiseptic. The most commonly used antiseptics are cresol (0.4 per cent), phenol (0.5 per cent), glycerin and organic mercury compounds.

*Immunity Reactions*—Immunity, in its broadest medical sense means resistance to disease or harm. The science of immunology however, is concerned chiefly with the specific reactions which occur after a preparation containing the microorganisms of an infectious disease or a complex substance composed of the products of growth of microorganisms or an animal product containing substances antagonistic to microorganisms or their products is introduced within the body.

The reactions of immunity may act either to prevent disease or to cure it, or to distinguish one disease from another. Accordingly, the products enumerated in this section may be used in prophylaxis, in treatment, or in diagnosis. Immunity may be natural to the individual or it may be acquired. That which is called into play by the use of these products is of course acquired immunity.

There is a further classification of acquired immunity into passive and active forms. In active immunity, the agents which actually perform the protective work are created within the body. In passive immunity, these agents are introduced ready formed from without. This gives us a basis for the classification of the therapeutic products. Those of the first class, the serums, and the antitoxins, which are derived from the serums are intended to produce passive immunity, they are 'antibodies' which directly antagonize the invading bacteria, viruses and toxins.

The other great class of immunity products is called "antigens" because they are administered in the hope that their presence in the body will stimulate the production of antibodies.

The active immunity, formed by the introduction of antigens is in general slower in appearance but more lasting than the

passive immunity caused by the introduction of foreign antibodies. It must be remembered also that the antigen is of the same nature as the organism causing the disease which is to be combated, and that in using antigens we are calling on the cells and fluids of the individual to produce their own protecting substances. To the class of antigens belong bacterial and viral vaccines, toxins, and toxoids.

These antigens and antibodies are not usually absorbed, without change, from the gastrointestinal tract. Hence, they must be administered by the intracutaneous, subcutaneous, intramuscular, intraspinal, or intravenous route in order to reach tissues not directly accessible.

The use of serums and serum preparations is sometimes followed by certain untoward manifestations. These are due usually to sensitivity of the individual to animal products especially horse serum and in certain cases may be avoided by the use of serums which have been altered by the action of enzymes or by using serums from the bovine species or from sheep or goats. Serums and antitoxins, unless made by the inoculation of the horse, must show on the label the species of animal used. The following outline sets forth the classification of the preparations as described in this chapter.

## SERUMS

### NORMAL SERUMS OR NORMAL BLOOD DERIVATIVES

- Citrated normal human plasma
- Human immune globulin
- Normal human serum

### IMMUNE SERUMS

#### *Antitoxic serums*

#### *Antitoxins*

- Antivenin (*Crotalus*)
- Botulism antitoxin
- Diphtheria antitoxin
- Diphtheria antitoxin, Bovine
- Diphtheria antitoxin, globulin-modified
- Erysipelas streptococcus antitoxin
- Gas gangrene antitoxin (*Cl. perfringens* and *Cl. septicum*)
- Gas gangrene antitoxin (*Cl. perfringens*, *Cl. septicum*, *Cl. novyi*, *Cl. bifermentans* and *Cl. histolyticum*)
- Tetanus-gas gangrene antitoxin (*Cl. welchii*, *Cl. septicum* and *Cl. tetani*)
- Meningococcus antitoxin
- Scarlet fever streptococcus antitoxin
- Staphylococcus antitoxin
- Tetanus antitoxin
- Tetanus antitoxin, Bovine

*Antibacterial serums*

Antianthrax serum	
Antidysenteric serum	
Antierysipelas serum	
Antierysipeloid serum	
Antimeningococcic serum	
Antipneumococcic serums	
Antipneumococcic horse serum	Type I
Antipneumococcic horse serum	Type II
Antipneumococcic horse serum	Types I and II combined
Antipneumococcic horse serum	Types IV and VIII combined
Antipneumococcic horse serum	Types V and VII
Antipneumococcic horse serum	Type VII
Antipneumococcic rabbit serum	Type I
Antipneumococcic rabbit serum	Type II
Antipneumococcic rabbit serum	Type III
Antipneumococcic rabbit serum	Type V
Antipneumococcic rabbit serum	Type VII
Antipneumococcic rabbit serum	Type VIII
Antipneumococcic rabbit serum	Type XIV

## NATURAL PRODUCED ANTIBODIES

- Human measles immune serum
- Human scarlet fever immune serum

## VACCINES

Active immunization General considerations

## ATTENUATED LIVING VIRUSES OR KILLED VIRUSES

- Rabies vaccine
- Rabies vaccine (Cumming)
- Rabies vaccine (Harris)
- Rabies vaccine (Pasteur)
- Rabies vaccine (Semple)
- Rabies vaccine (Semple) chloroform killed

## BACTERIAL TOXINS

- Scarlet fever streptococcus toxin

## BACTERIAL TOXINS MODIFIED

- Diphtheria toxin antitoxin mixture
- Diphtheria toxoid
- Diphtheria toxoid alum precipitated refined
- Diphtheria toxoid tetanus toxoid alum precipitated combined
- Staphylococcus toxoid
- Tetanus toxoid

## BACTERIAL VACCINES

- Bacterial vaccine made from the acne bacillus
- Bacterial vaccine made from *Brucella melitensis*, *abortus* or *suis* (Undulant Fever vaccine)
- Bacterial vaccine made from the cholera vibrio
- Bacterial vaccine made from the plague bacillus
- Bacterial vaccine made from staphylococci
- Bacterial vaccine made from the typhoid bacillus
- Bacterial vaccine made from the typhoid bacillus and the paratyphoid "A" and "B" bacilli

## DIAGNOSTIC AGENTS

## Tuberculins

- Purified protein derivative of tuberculin
- Old tuberculin
- New tuberculin, B. E.
- New tuberculin, B. E., dried
- New tuberculin, T. R.
- New tuberculin, T. R., dried
- Tuberculin Denys

## SERUMS

## Normal Serums or Normal Blood Derivatives

This section lists those preparations derived from normal blood, such as plasma, serum or globulins. Any antibodies which the preparations may contain have been produced naturally in the body. There is some evidence that human serum preparations may, in a manner not understood, be instrumental in leading to the development of a form of infectious jaundice. They may also lead to reactions of the type usually regarded as allergic.

**HUMAN IMMUNE GLOBULIN.**—Measles Prophylactic.—Placental Extract.—"A sterile solution of antibodies obtained from the placentae expelled by healthy women (*Homo sapiens*). Each preparation shall be composed of a pool from at least ten individuals. Human immune globulin complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and standards see the U. S. Pharmacopeia under Globulinum Immune Humanum.

**Actions and Uses.**—Human immune globulin is useful in the prevention and modification of measles. It is equivalent in usefulness to convalescent serum but has the advantage of universal

availability. It has the disadvantage of producing reactions not always mild. Most reactions, however, can be avoided by the administration of the proper dosage, which is necessarily modified in accordance with the stage of the incubation period or the prodromal stage of the disease. It is useful in the prevention of measles in institutional cases in larger doses than those given for modification. Prevention is, of course, less desirable than modification except where younger children ill with other diseases are apt to contract measles by exposure to a modified case. Otherwise it is more desirable to permit a child to have mild measles so that immunization occurs rather than to prevent the disease and leave the child nonimmune to subsequent attacks of the disease. Protection should not be attempted until definite exposure has taken place. Attempts to avoid reactions have led to refinement and concentration of the product and even to its oral administration, the latter cannot be advocated on the basis of the evidence which is available at present.

**Dosage**—The amount of human immune globulin which should be injected in a given case depends on the following factors:

- 1 Whether modification or prevention is desired
- 2 The age and general condition of the patient
- 3 The intimacy of exposure

Careful consideration of the available literature is necessary to evaluate properly these factors and determine an entirely satisfactory dosage, and even then it is not always possible to be certain of not obtaining prevention when modification is desired and vice versa. The following doses are recommended merely as a general pattern and are subject to adjustment in accordance with the factors listed above: for prevention 2 to 10 cc; for modification, 2 to 5 cc.

#### THE GILLILAND LABORATORIES, INC.

Immune Globulin (Human). 2 cc and 10 cc vials. Preserved with 0.1 per cent of phenol and 0.01 per cent of merthiolate.

#### LEDENLE LABORATORIES, INC.

Immune Globulin (Human). 2 cc and 10 cc vials. Preserved with 0.5 per cent of phenol.

#### THE NATIONAL DRUG CO.

Immune Globulin (Human). 2 cc and 10 cc syringes and 2 cc and 10 cc ampul vials. Preserved with merthiolate 1:4000.

#### PITMAN MOORE COMPANY

Immune Globulin (Human). 2 cc and 10 cc diaphragm stoppered vials. Preserved with merthiolate 1:7500.



## PARKE, DAVIS &amp; COMPANY

**Immune Globulin (Human):** 2 cc. and 10 cc vials Preserved with 0.1 per cent of merthiolate

## SHARP &amp; DOHME, INC.

**Immune Globulin (Human):** 2 cc and 10 cc ampul-vials Preserved with 0.5 per cent of phenol

**Vacule Ampoule-Vials Lyovac Immune Globulin (Human):** Containing amounts sufficient to yield 2 cc and 10 cc. of restored globulin, packaged respectively with 2 cc. and 10 cc. ampuls of distilled water as a diluent, preserved with 0.35 per cent phenol. A dried form of immune globulin (human)

## E. R. SQUIBB &amp; SONS

**Immune Globulin (Human):** 2 cc. and 10 cc. vials Preserved with merthiolate, 1:10,000, and 0.2 per cent of phenol

**CITRATED NORMAL HUMAN PLASMA.**—Normal Human Plasma—"Citratd Normal Human Plasma is the sterile plasma obtained by pooling approximately equal amounts of the liquid portion of citrated whole blood from eight or more humans (*Homo sapiens*) who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood transfusion at the time of drawing the blood. Each bleeding is drawn under aseptic precautions into individual 50 cc. of a sterile, 0.9 per cent sodium chloride solution. The cells of sodium citrate solution are transferred to a pool by means of a closed system. Sterility tests are made, a preservative is added, and the plasma is distributed into final containers through a closed system. Citrated normal human plasma complies with the requirements of the National Institute of Health of the United States Public Health Service.

Citrated normal human plasma may be dispensed as liquid plasma, as frozen plasma, or as dried plasma. Citrated normal human plasma must be free from harmful substances detectable by animal inoculation, and must not contain an excessive amount of preservative" U. S. P.

For description and standards see the U. S. Pharmacopoeia under Plasma Humanum Normale Citratum

**Actions and Uses**—Citrated normal human plasma is administered in the treatment of surgical and traumatic shock, in the treatment of burns when loss of available plasma occurs, to combat hypoproteinemia, and as a temporary substitute for whole blood in the treatment of hemorrhage when whole blood is not immediately available. Plasma and serum may be considered satisfactory substitutes for whole blood *except in those cases in which the administration of red blood corpuscles is regarded as essential*

**Dosage**—Citrate normal human plasma whole or restored is administered intravenously in amounts equivalent to those employed in the transfusion of whole blood but it should be remembered that plasma represents approximately one half the total volume of whole blood. Average dose is 500 cc intravenously (U S P)

#### CUTLER LABORATORIES

**Normal Human Plasma** 50 cc and 300 cc bottles  
1 10 000 sodium ethylmercuri thiosalicylate is used as a preservative

#### SAMUEL DLUTSCH SERUM CENTER MICHAEL REESE HOSPITAL

**Normal Human Plasma (Citrate)** 300 cc bottle Phenyl mercuric borate 1 15 000 is used as a preservative contains dextrose in final concentration of 5 per cent

**Normal Human Plasma (Citrate) (Diluted)** 300 cc bottle Diluted with 250 cc of isotonic solution of sodium chloride Phenyl mercuric borate 1 15 000 is used as a preservative contains dextrose in final concentration of 5 per cent

#### SHARP & DOHMEYER INC

**Vacule Ampul-Vial Lyovac Normal Human Plasma**  
Containing a sufficient amount of rapidly lyophilized human blood plasma (preserved to yield 250 cc of rest ampule of distilled water phenylmercuric borate),

**Vacule Ampul-Vial Lyovac Normal Human Plasma**  
Containing an amount (preserved with phenyl mercuric borate 1 25 000) to yield 50 cc of restored plasma, packaged with a 50 cc bottle of distilled water as a diluent (preserved with phenyl mercuric borate 1 100 000)

#### NORMAL HUMAN SERUM—Human Serum—Nor

mal Human Serum  
approximately equal to  
whole blood from  
have been certified  
any disease when  
time of drawing the blood Each bleeding is drawn under  
aseptic precautions into individual sterile centrifuge bottles and  
allowed to coagulate for at least 12 hours and not more than  
24 hours The cell free serum is separated by centrifugation  
and transferred to a pool by means of a closed system Sterility  
tests are made a preservative is added the serum is passed  
through a bacteria excluding filter and finally distributed into  
the final containers through a closed system Normal Human  
Serum complies with the requirements of the National Institute  
of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia under Serum Humanum Normale

*Action, Uses and Dosage*—See Citrated normal human plasma.

#### CUTTER LABORATORIES

Normal Human Serum: 50 cc and 250 cc bottles 1-10,000 sodium ethylmercuri-thiosalicylate is used as a preservative

#### SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE HOSPITAL

Normal Human Serum: 250 cc. bottle. Phenyl mercuric borate 1:15,000 is used as a preservative

Normal Human Serum (Diluted): 250 cc. bottle. Diluted with 250 cc. of isotonic solution of sodium chloride. Phenyl mercuric borate 1:15,000 is used as a preservative.

### Immune Serums for Prophylactic or Therapeutic Purposes

#### ANTITOXIC SERUMS

Antibodies are usually directed against the toxins or other soluble products of bacteria or against the bacteria themselves. All the antibodies enumerated below are formed in the blood serum of the larger domestic animals by active immunization, that is, by injecting the animal with an antigen. The animal is then bled to furnish the serum, which afterward may be purified, in the case of the antitoxins and some other immune serums, to remove as many inactive substances as possible, leaving the antibody in a concentrated form.

#### ANTITOXINS

The antitoxins are among the most useful of the antibodies. As the name implies, they antagonize toxins. Though toxins may be secreted by plants other than the bacteria and by some animals, e. g., the snake, the typical toxins are the soluble poisons produced by diphtheria and tetanus bacilli.

Diphtheria and tetanus are dangerous diseases almost entirely on account of the action of these toxins, and conversely, their prevention or cure, when the organisms have once gained entrance to the body, depends on the work of the particular antitoxin. Though the presence of the toxin stimulates the body to produce antitoxin, this active immunity may not be enough to save life, and, at any rate, assistance by the injection of antitoxin, ready made in the blood serum of another animal, hastens the cure or may prevent the disease.

In some individuals, eruptions occur after injection of antitoxin, rarely swelling and pain in the joints; in others, more severe symptoms have been observed and in a few instances sudden death has occurred. These conditions are due, not to the antitoxin but to the horse serum in which it is contained.

**ANTIVENIN (CROTALUS)—CROTALUS ANTITOXIN—NORTH AMERICAN ANTI-SNAKE BITE SERUM**—An antitoxic serum prepared by immunizing animals against the venom of snakes of the crotalus family

*Actions and Uses*—Tests on animals show that the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Crotalus antitoxin is used to neutralize the venom injected by the bite inflicted by members of the crotalus family

*Dosage*—The serum is administered intramuscularly or subcutaneously in cases seen late or in the presence of severe symptoms it may be administered intravenously. Certain observations seem to show that there is great advantage in giving the serum in the vicinity of the bite. Use of the antitoxin never should be allowed to replace first aid measures especially local incisions and suction. Perhaps 50 cc of serum is as small an amount as is likely to prove beneficial

SHARP & DOHME, INC

**Vacule Ampul Vial Lyovac Antivenin (Nearctic Crotalidae) Polyvalent** Containing a sufficient amount of lyophilized antivenin to yield 15 cc of the serum packaged with a 15 cc syringe of distilled water as a diluent preserved with 0.35 per cent of phenol a 1 cc ampul vial of normal horse serum (diluted 1:10) as test and desensitizing material and a first aid ampul of iodine solution. A dried form of antivenin (crotalus) antitoxic serum

A lyophilized antitoxic serum prepared by injecting horses with venoms from serpents of the North American species of the family Crotalidae (rattlesnake venoms 90 per cent moccasin venoms 10 per cent. Moccasin venoms include both the cotton mouth moccasin and the upland moccasin or copperhead)

The process of lyophilization consists in the following. The antivenin in specially designed final containers is rapidly frozen by immersion in a freezing mixture to convert the substance with the least molecular rearrangement. The container is then subjected to a high vacuum to accomplish dehydration which is continued until the residual moisture content is less than 1 per cent

**BOTULISM ANTITOXIN**—An antitoxic serum prepared by immunizing animals against two types of the toxin of *Clostridium botulinum*

*Actions and Uses*—For prophylaxis and treatment of botulism. The clinical value of the antitoxin is uncertain

*Dosage*—Prophylactic subcutaneous injections of not less than 2500 units of bivalent antitoxin. Therapeutic intravenous injection of not less than 10000 units of the bivalent antitoxin to be repeated as indicated by the nature of the case

*Preparation*—

This antitoxin is prepared by the hyperimmunization of horses by continued and progressively increasing doses of botulinus toxin. Separate animals are injected with type A and with type B toxin and

the commercial product is prepared by mixing given quantities of each type so that each marketed package will contain 2,500 units each of type A and type B antitoxin. The technic used in preparation and the standard of unitage are in conformity with requirements of the National Institute of Health.

The product consists of the whole serum as derived from the defibrinated blood by process of centrifugation and Berkefeld filtration.

#### JENSEN-SALSBERG LABORATORIES, INC.

**Botulinus Antitoxin:** Vial containing 2,500 units each of type A and type B botulism antitoxin. Preserved with phenol 0.5 per cent, glycerin 0.5 per cent and sodium citrate 1 per cent.

**DIPHTHERIA ANTITOXIN.**—Purified Antidiphtheric Serum.—Concentrated Diphtheria Antitoxin.—Antidiphtheric Globulins.—“Diphtheria Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against diphtheria toxin. After the serum or plasma from the immunized animal has been collected, the antitoxin-bearing globulins are separated from the other constituents of the serum or plasma by the addition of calcium chloride and a precipitant, the mixture is filtered through a Berkefeld filter, and the filtrate is adjusted to a specific gravity of 1.020. The product complies with the requirements of the National Institute of Health of the United States Public Health Service.” *U S P*

For description and standards see the *U S Pharmacopeia* under *Antitoxinum Diphthericum*.

**Actions and Uses.**—For prophylaxis and treatment of diphtheria.

**Dosage.**—By parenteral injection therapeutic, 20,000 units, prophylactic, 1,000 units.

**DIPHTHERIA ANTITOXIN, BOVINE.**—An antitoxin differing from diphtheria antitoxin in general use in that it is made from the serum of cattle instead of from horse serum and has a somewhat lower potency.

**Actions and Uses.**—Diphtheria antitoxin, bovine, serves as an alternative to diphtheria antitoxin usually used (equine) in the treatment of individuals giving immunological evidence of, or a history of sensitivity to horse serum.

**Dosage.**—Since diphtheria antitoxin, bovine, contains fewer units per cubic centimeter than the antitoxin prepared from horse serum, a larger volume must be injected.

**DIPHTHERIA ANTITOXIN, GLOBULIN-MODIFIED.**—A preparation differing from diphtheria antitoxin *U S P* chiefly in the method of refinement.

The process of refinement is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin. As a result of this process, as much

as 90 per cent of the coagulable protein may be digested a smaller portion is precipitated, and the remainder, a pseudo-globulin fraction, is purified first by ordinary filtration and then by ultrafiltration and dialysis

*Actions, Uses and Dosage*—Same as for diphtheria antitoxin U S P

#### LEDERLE LABORATORIES, INC

**Diphtheria Antitoxin, Globulin-Modified** Syringes containing 40 000 units and vials containing 1 000 5 000 10 000 20 000 and 40 000 units

#### ERYSIPELAS STREPTOCOCCUS ANTITOXIN—

An antitoxic serum prepared by immunizing horses with the toxin or the toxin and cultures of the hemolytic streptococci usually isolated from erysipelas lesions. The serum usually is concentrated in a manner similar to that employed for other antitoxins

*Actions and Uses*—Reports have been published which suggest that the injection of erysipelas streptococcus antitoxin favorably affects the course of erysipelas. Since valuable chemotherapeutic preparations have been available this antitoxin is rarely used. It probably is of little value.

*Dosage*—There is no established dosage. Quantities recommended by various manufacturers vary from 12 cc to 100 cc to be repeated according to the influence or want of influence on the course of the infection.

#### LEDERLE LABORATORIES, INC

**Erysipelas Streptococcus Antitoxin, Globulin Modified** Vial containing 1 therapeutic dose. An antitoxin prepared by immunizing horses with the toxin from typical strains of streptococci isolated from erysipelas lesions and from the well known scarlet fever strain Dochez N Y 5 which is refined by a controlled method of selective digestion of the protein of the immune horse blood with pepsin.

#### THE NATIONAL DRUG CO

**Erysipelas Streptococcus Antitoxin (Refined and Concentrated Globulin)** Syringe containing 4 000 units packaged with a 1 cc ampul vial of a 1:10 dilution of antitoxin to determine protein sensitivity of the patient and for early doses of antitoxin to sensitive patients. An antitoxin prepared by immunizing horses against strains of virulent erysipelas streptococci (Birkhaug and others).

#### PARKE DAVIS & COMPANY

**Erysipelas Streptococcus Antitoxin, Refined and Concentrated** 10 cc and 20 cc. syringes. An antitoxin prepared by immunizing horses with the toxin and cultures of streptococci isolated from erysipelas cases.

## U. S. STANDARD PRODUCTS CO.

**Erysipelas Streptococcus Antitoxin** (Refined and Concentrated): Syringe containing the average initial therapeutic dose (approximately 15 cc.). An antitoxin prepared by immunizing horses with the toxin and cultures of streptococci isolated from erysipelas cases, preserved with 0.4 per cent cresol.

**GAS GANGRENE ANTITOXIN.**—An antitoxic serum prepared by immunizing horses with the toxins of *Cl. perfringens* (welchii) and *Cl. septicum* (Watson septicum). After the desired degree of potency is obtained, the horses are bled, the fluid portion of the blood separated from the cellular elements, and the serum prepared in a manner similar to that used for other antitoxic serums. Potency is determined according to the methods described by the National Institute of Health.

**Actions and Uses.**—Used in prevention and treatment of gas gangrene. The clinical value of this antitoxin is questionable.

**Dosage.**—Therapeutic: 10,000 to 40,000 units each of *Cl. perfringens* and *Cl. septicum* intramuscularly or intravenously, preferably the latter, repeated every twelve to twenty-four hours depending on the symptoms in the individual case.

## CLIFFER LABORATORIES

**Gas Gangrene Antitoxin:** Bottle containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.35 per cent cresol.

## THE GILLILAND LABORATORIES, INC.

**Gas Gangrene Antitoxin, Concentrated and Refined:** Syringe and vial each containing 10,000 units of *Cl. perfringens* and 10,000 units of *Cl. septicum* antitoxins, and packaged with a 1 cc. vial of dilute (1:10) antitoxin for determination of sensitivity to horse serum protein.

## THE NATIONAL DRUG CO.

**Gas Gangrene Antitoxin Refined and Concentrated:** Syringe or vial containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins.

## PARKE, DAVIS &amp; COMPANY

**Gas Gangrene Antitoxin Refined and Concentrated (Combined):** Syringe and vial each containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins.

## SITARP &amp; DOTME, INC.

**Gas Gangrene Antitoxin Concentrated (Combined):** Syringe containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins.

**Gas Gangrene Antitoxin Unconcentrated (Combined):** Bottle containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins.





## CUTTER LABORATORIES

**Tetanus-Gas Gangrene Antitoxin:** Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.35 per cent tricresol.

## THE GILLILAND LABORATORIES, INC.

Concentrated and  
1,500 units of tetanus  
*fringens* and *Cl. sep-*  
vial of dilute (1:10)  
antitoxin for determination of sensitivity to horse protein

## LEDERLE LABORATORIES, INC.

**Tetanus-Gas Gangrene Antitoxin, Globulin Modified:** Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins

## ELI LILLY AND COMPANY

**Tetanus-Gas Gangrene Antitoxin (Combined):** Syringe containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins

## THE NATIONAL DRUG CO

**Tetanus-Gas Gangrene Antitoxin:** Syringe and ampule vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins

## PARKE, DAVIS &amp; COMPANY

**Tetanus-Gas Gangrene Antitoxin, Refined and Concentrated (Combined):** Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins

## SHARP &amp; DOHME, INC.

**Tetanus-Gas Gangrene Antitoxin Mixed:** Syringe and ampul-vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins

## E. R. SQUIBB &amp; SONS

**Tetanus-Gas Gangrene Antitoxin:** Vial containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 1:20,000 merthiolate and 0.25 per cent of phenol.

## U. S. STANDARD PRODUCTS CO.

**Tetanus-Gas Gangrene Antitoxin, Refined and Concentrated:** Syringe containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins

**MENINGOCOCCUS ANTITOXIN**—An antitoxin prepared by the immunization of animals to polyvalent filtrates of six to eight day hormone broth cultures of the four Gordon groups of meningococcus, after the method of Ferry, Norton and Steele. The antitoxin is standardized by human skin tests a skin test dose being that amount of toxin which will produce a local skin reaction of at least 10 mm in diameter when injected intradermally in susceptible individuals. The unit of antitoxin is ten times that amount which, when mixed with one skin test dose of toxin, will produce a negative reaction or one appreciably less than 10 mm in diameter.

*Actions and Uses*—The published studies on the effect of

cations and its mortality rate may all be favorably affected by the timely and proper administration of the antitoxin. Its clinical value is questionable. With the introduction of new chemiotherapeutic agents, the use of this antitoxin has been supplemented or supplanted by these newer agents. It should not be used routinely.

*Dosage*—Dependent on the condition of the patient, the degree of toxemia, the occurrence of complications and whether child or adult, 20 000 to 30 000 units (60-100 cc.) in 120-200 cc. of physiological solution of sodium chloride may be administered intravenously (injected slowly). This may be repeated daily if required. These doses (60-100 cc.) may be given intramuscularly, but it is (probably) a less effective route.

Dependent on the same factors and also on the volume of spinal fluid withdrawn 6 000-12 000 units (20-40 cc.) may be injected intraspinally or intracisternally, but many experienced observers advise against intrathecal administration. This procedure may be repeated daily if required. The usual case is said to require a total of from 50 000 to 100 000 units.

**PARKE, DAVIS & COMPANY**

**Meningococcus Antitoxin** Vial containing 10 000 units. An antitoxin prepared by immunizing horses to bacteria free meningococcus toxin, standardized to contain not less than 350 units of antitoxin per cubic centimeter. Preserved with 0.3 per cent of tricresol.

**SCARLET FEVER STREPTOCOCCUS ANTITOXIN**—Scarlet Fever Antitoxin—Refined Scarlet Fever Antitoxin—Anti Scarlet Fever Globulins—Scarlet Fever Streptococcus Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against the toxin.

produced by the streptococcus regarded as causative of scarlet fever. Scarlet Fever Streptococcus Antitoxin has a potency of not less than 400 anti-toxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service 'U. S. P.'

For description and standards see the U. S. Pharmacopoeia under Antitoxinum Scarlatinae Streptococcum.

*Actions and Uses*—There is satisfactory evidence that scarlet fever is caused by hemolytic streptococci and that the administration of a serum containing the antitoxin produced by these organisms favorably influences the course of scarlet fever. It is also believed that temporary immunity against scarlet fever may be established through the use of such a serum, but the prophylactic use generally is not considered advisable. The serum is also used to distinguish the rash of scarlet fever from other rashes by the production of a blanched area at the site of its intradermal injection.

*Dosage*—Prophylactic, 3,000 U. S. P. H. S. units, therapeutic, 9,000 U. S. P. H. S. units.

**THE GILLILAND LABORATORIES, INC.**

Scarlet Fever Streptococcus Antitoxin (Refined and Concentrated): Syringes containing 3,000 and 9,000 units respectively.

**LEIBERLE LABORATORIES, INC.**

Scarlet Fever Streptococcus Antitoxin, Globulin Modified: Vials containing 3,000 and 9,000 units respectively.

**THE NATIONAL DRUG CO.**

Scarlet Fever Streptococcus Antitoxin, Refined and Concentrated: Syringes containing 3,000 and 9,000 units, respectively.

**PARKER, DAVIS & COMPANY**

Scarlet Fever Streptococcus Antitoxin: Syringes containing 3,000 and 9,000 units, respectively.

**SHARP & DOWME, INC.**

Scarlet Fever Streptococcus Antitoxin Concentrated: Syringes containing 3,000 and 9,000 units, respectively.

**E. H. SQUINN & SONS**

Scarlet Fever Streptococcus Antitoxin Concentrated: Syringes containing 3,000 and 9,000 units, respectively. Preserved with 1:2000 formaldehyde and 0.2% per cent of alcohol.

**STAPHYLOCOCCUS ANTITOXIN**—A vaccine prepared by the use of a special method for the production of a vaccine from the staphylococcus aureus. The vaccine is a white, granular, sterile substance of the consistency of cream when mixed with sterile distilled water.

ment Commission on Biological Standardization of the Health Organization of the League of Nations in 1934, the unit being the equivalent to approximately 125 original antidermonecrotic units, an antidermonecrotic unit being that amount of antitoxin required to neutralize one necrotizing dose of staphylococcus toxin.

*Actions and Uses*.—Staphylococcus antitoxin is suggested in the treatment of acute and severe staphylococcic infections with or without septicemia. Its use in treatment calls for adequate dosage administered early. Most of the antitoxin estimated to be necessary for the entire treatment of the infection should be injected during the first few hours after decision is made to use the serum. Supplementing the use of antitoxin in the more severe types of staphylococcic infections, surgical drainage of accessible foci and transfusions with normal or immune donors should be a part of the treatment. Probably chemotherapeutic preparations should take precedence over this antitoxin in routine treatment.

*Dosage*.—For the treatment of localized infections, 10,000 units. For the treatment of more severe infections, from 30,000 to 100,000 units early during the first day in divided doses, followed by from 20,000 to 100,000 units daily until the pulse rate and temperature have subsided and the blood cultures are sterile for three consecutive days.

**LEDERLE LABORATORIES, INC**

**Staphylococcus Antitoxin, Globulin-Modified** Vials containing 10,000 and 20,000 units, respectively

**TETANUS ANTITOXIN**—Purified Antitetanic Serum—Concentrated Tetanus Antitoxin.—Refined Tetanus Antitoxin.—Antitetanic Globulins.—Tetanus Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against tetanus toxin. After the serum or plasma from the immunized animal has been collected, the antitoxin bearing globulins are separated from the other constituents of the serum or plasma and dissolved in freshly distilled water. Sodium chloride and a preservative are then added and the solution is filtered through a bacteria excluding filter. Tetanus antitoxin has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service "U S P".

For description and standards see the U S Pharmacopeia under Antitoxinum Tetanicum.

*Actions and Uses*.—Tetanus antitoxin is highly effective in the prevention of tetanus, but its effectiveness when used in the treatment of the disease is much less certain.

*Dosage*.—By parenteral injection therapeutic, 20,000 units prophylactic, 1,500 units. Intrathecal administration generally is regarded as inadvisable.

## PITMAN-MOORE COMPANY

**Tetanus Antitoxin, Pepsin Digestion Refined:** Vials containing 1,500 units and syringes containing 1,500 units and 10,000 units respectively. The antitoxin differs from tetanus antitoxin-U. S. P. chiefly in the method of refinement, which is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin.

**TETANUS ANTITOXIN BOVINE.**—An antitoxin complying with the standards for tetanus antitoxin-U. S. P., except that it is made from the serum of cattle instead of from the more generally used horse serum. It may be used in the treatment of individuals giving immunological evidence of, or a history of sensitivity to, horse serum.

*Actions, Uses and Dosage.*—Same as for Tetanus Antitoxin.

## THE GILLILAND LABORATORIES, INC.

**Tetanus Antitoxin (Bovine):** Vials containing 1,500 and 10,000 units, respectively.

## SHARP &amp; DOHME, INC.

**Vacufe Ampul-Vials Lyovac Tetanus Antitoxin (Bovine):** Containing sufficient amounts of lyophilized antitoxin to yield 3 cc. (1,500 units) and 20 cc. (10,000 units) of the antitoxin, packaged respectively with 3 cc. and 20 cc. ampuls of distilled water for dilution, and with a 1 cc. ampul-vial of normal bovine serum (1:10 dilution) for sensitivity tests.

## ANTIBACTERIAL SERUMS

More complex in action than the antitoxin and in general less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. They are believed to act primarily by combining chemically with antigens on the bacterial surfaces, thereby rendering the bacteria susceptible to phagocytosis by polymorphonuclear and mononuclear leukocytes. The sphere of usefulness of the antibacterial sera is open to much discussion, and is in need of constant reevaluation in particular with the progress of chemotherapy with the sulfonamide drugs.

**ANTIANTHRAX SERUM.**—Serum Antianthraxicum. —A serum prepared by immunizing horses against virulent anthrax bacilli (*Bacillus anthracis*).

*Actions and Uses.*—Good results have generally been reported from the use of the specific serum in human anthrax. Protective antibodies can be demonstrated experimentally.

*Dosage.*—Minimum of 50 cc. intramuscularly or intravenously. Local subcutaneous injection is sometimes employed. The serum should be used as early as possible and used freely, the dose being repeated several times a day in severe cases.

**LEDERLE LABORATORIES, INC****Antianthrax Serum 50 cc vial****PARKE, DAVIS & COMPANY****Antianthrax Serum 50 cc syringe**

**ANTIDYSENTERIC SERUM** — Serum Antidysentericum — The serum (polyvalent) of horses immunized against the Shiga bacillus (*Shigella dysenteriae*), its products of growth and other types of the dysentery bacilli. Probably chemotherapeutic preparations should take precedence over this antitoxin in routine treatment.

*Actions and Uses* — A reduction in the mortality rate of bacillary dysentery through the use of some serums has been reported by some observers but not confirmed by all. It would seem that the best results may be ascribed to an antitoxic action in infections with the Shiga Kruse type of bacillus. Infections with the Flexner, Harris or Hiss Y strains, which are relatively poor in toxin production have not been so favorably affected though some bactericidal action is claimed. The most favorable results are observed in the early stage of the disease.

The serum is required to show a high agglutinin titer for the various types of dysentery bacilli.

*Dosage* — From 20 to 100 cc, subcutaneously or intramuscularly.

**LEDERLE LABORATORIES, INC**

**Antidysenteric Serum (Polyvalent) Refined and Concentrated** Vial containing 10000 units of Shiga antitoxin together with antibacterial antibodies for the Shiga and Flexner types.

**ANTIERYSIPELAS SERUM** — Erysipelas antistreptococcic serum. A serum containing the antibodies and antibacterial properties for hemolytic streptococci from erysipelas.

The serum is obtained from horses immunized with strains of hemolytic streptococci obtained from human cases of erysipelas. It is concentrated by a method similar to that employed in the refinement of diphtheria antitoxin; the resultant serum containing both neutralizing and bacterial antibodies.

*Actions, Uses and Dosage* — For therapeutic use against erysipelas. It may be of value when administered in adequate doses in the early stages of the disease. Since valuable chemotherapeutic preparations have been available this serum is rarely used. It probably is of little value.

**ELI LILLY AND COMPANY**

**Erysipelas Antistreptococcic Serum (Concentrated)** Syringe containing one average initial therapeutic dose.

**ANTI-ERYSIPELOID SERUM.**—A serum containing the antibodies and antibacterial properties for *Erysipelothrix rhusiopathiae* (suis). The serum is prepared from horses subjected to increasing subcutaneous injections of live cultures of the organism. Potency is tested on pigeons in which 0.1 cc. of the serum protects against infection lethal to controls in from three to four days.

**Actions and Uses.**—For treatment of the clinical condition known as erysipeloid, which is not to be confused with erysipelas.

**Dosage.**—It is suggested that from 10 to 20 cc. be administered subcutaneously or intramuscularly and quantities of 0.25 to 0.5 cc. at numerous places about the border of the lesion.

JENSEN-SALSBERY LABORATORIES, INC.

**Anti-Erysipeloid Serum:** 20 cc. vial. Preserved with 0.5 per cent of phenol, 0.5 per cent of glycerin and 10 per cent of sodium citrate.

Approved by the United States Food and Drug Administration

"This product is the United States Food and Drug Administration's requirements of the National Institute of Health of the United States Public Health Service" U S P

For description and standards see the U S Pharmacopoeia under Serum Antimeningococcicum.

The product may be concentrated in a manner similar to the concentration of diphtheria antitoxin.

**Actions and Uses.**—There is much doubt as to the value of antimeningococcic serum and it should not be used routinely. With the introduction of new chemotherapeutic agents the use of the serum has been supplemented or supplanted by these newer agents. Serologic (test tube) tests have been employed for determining the potency of antimeningococcic serum but there is no conclusive evidence that they measure the clinical usefulness of the product.

**Dosage.**—Intravenous administration of this serum has generally replaced intrathecal use, dose intravenous 50 cc. for children and up to 100 cc. for adults. When used intrathecally average dose for adults, 30 cc. as early as possible in the disease, repeated as indicated, for children, doses up to 20 or 30 cc. depending upon the amount of spinal fluid that can be withdrawn and the amount of serum that can be administered without untoward symptoms. The serum should be introduced slowly by gravity after the removal of a corresponding amount of spinal fluid. Administration should be controlled by blood pressure readings, a drop of 10 mm. of mercury during the administration being the signal for withdrawal of the needle. Intravenous route is especially indicated. In very early cases

or in those cases accompanied by frank meningococcemia as demonstrated by positive blood cultures, or by hemorrhagic rash, but even in these a chemotherapeutic agent should be the first choice unless some absolute contraindication exists. Many experienced observers advise against intrathecal administration.

#### **THE GILLILAND LABORATORIES, INC**

**Antimeningococcic Serum, Concentrated and Refined** 10 cc vials with or without attachments for intraspinal administration, packaged with a vial of a 1:10 dilution of the serum for determining the sensitivity of the patient. An antimeningococcic serum which has been refined, and the antibodies so concentrated that 10 cc is equal to at least 40 cc. of the whole (unrefined) serum and therefore particularly suited for intraspinal injection. Preserved with 0.25 per cent phenol 0.005 per cent sodium ethylmercuri thiosalicylate.

#### **LENNER LABORATORIES, INC**

**Antimeningococcic Serum:** 15 cc and 30 cc cylinders for intraspinal injection

#### **SHARP & DOHME, INC**

**Vacule Ampul-Vial Lyovae Antimeningococcic Serum Natural Polyvalent** Containing an amount of lyophilized antimeningococcic immune natural serum sufficient to yield 15 cc of restored serum in double concentration, packaged with a 15 cc ampul of distilled water for dilution, preserved with 0.35 per cent of phenol, a complete intraspinal outfit and a 1 cc ampul-vial of normal horse serum (diluted 1:10) as test and desensitizing material.

#### **U S STANDARD PRODUCTS CO**

**Antimeningococcic Serum Polyvalent** 15 cc vial with apparatus for intraspinal injection, and 30 cc vial

#### **ANTIPNEUMOCOCCIC SERUM-TYPE SPECIFIC**

—Serum Antipneumococcicum — Antipneumococcus Serum — Pneumonia Serum — 'Antipneumococcic serum is obtained from the blood of an animal which has been immunized with cultures of a pneumococcus (*Diplococcus pneumoniae*) of one of the types for which a serum has been prepared and which has been standardized or is released by the National Institute of Health of the U S Public Health Service and complies with the requirements of that agency of the government 'U S P'

The immune serum is prepared from the blood of animals which have been immunized by repeated injections of virulent type specific pneumococci. The virulence of the pneumococci is maintained by frequent passage through mice. When trial bleeding shows the serum to have reached a sufficient degree of potency, the animals (usually horses or rabbits) are bled aseptically and the serum collected, refined and concentrated. After concentration the usual safety and sterility tests are



carried out in accordance with the requirements of the National Institute of Health. The potency of the product is expressed in terms of the unit, based on satisfactory protection tests in mice. The unit is  $\frac{1}{500}$  cc. of the control serum distributed by the National Institute of Health for type specific pneumococcus antibody

For description and standards see the U S Pharmacopeia under Serum Antipneumococcum

**Actions and Uses.**—Type specific antipneumococcic serums are useful primarily in the treatment of pneumococcic pneumonias, particularly when they are administered early in the course of the disease. Early specific diagnosis of the pneumococcus type involved has been facilitated since the advent of the improved Neufeld technic for typing. The use of this method has largely superseded the practice of administering combined serum of more than one of the common types in early cases of acute lobar pneumonia when rapid typing was not possible; only type specific serum can be expected to give a favorable response in the majority of cases. Pneumococci of many serological types may cause lobar pneumonia. Some 38 types and 12 additional subtypes are now recognized

In no case does the use of type specific serum justify the neglect of other therapeutic measures. In the treatment of pneumonia, chemotherapy should ordinarily be started at once. The decision whether or not to use serum in addition to chemotherapy will depend on circumstances in the individual case, usually serum will be required only in exceptional cases

Antipneumococcic serum obtained from rabbits has been shown to possess less of certain disadvantages accompanying the use of serum obtained from horses. Rabbit serum furnishes antibodies of smaller molecular size, which are therefore expected to penetrate infected tissues more readily. A method has been devised to minimize reactions, an attribute of nearly all natural (raw) rabbit serum. Chills are reportedly somewhat more common with unconcentrated than with concentrated rabbit

the oral administration

ately before the serum

• minary sensitivity tests

be performed

**Dosage**—"Average Dose—Parenteral, therapeutic, from 20,000 to 100,000 units" U. S. P.

Initial and subsequent dosage should be administered by such route, in such amount and at such intervals as indicated by

• judgment of the

may be curative

ic pneumococcic

• • • • • continuation with clinical observations to determine adequacy of dosage.

The following have been accepted by the Council, but there is evidence that some other type specific serums ("higher types") may be effective

**THE GILLILAND LABORATORIES, INC**

**Antipneumococcic Serum, Refined and Concentrated Type 1** Syringes containing 10 000 and 20 000 units respectively, each packaged with a vial of dilute serum (1/10) for the sensitivity test

**Antipneumococcic Rabbit Serum, Therapeutic, Type 1** Ampules containing 20 000 and 50 000 units respectively

**Antipneumococcic Serum, Refined and Concentrated Type 2** Syringes containing 10 000 and 20 000 units, respectively, each packaged with a vial of dilute serum (1/10) for the sensitivity test

**Antipneumococcic Rabbit Serum, Therapeutic, Type 2** Ampuls containing 20 000 and 50 000 units respectively

**Antipneumococcic Serum, Refined and Concentrated Types 1 and 2** Syringes containing 10 000 and 20 000 units each of Type I and Type II respectively, each packaged with a vial of dilute serum (1/10) for the sensitivity test

**Antipneumococcic Rabbit Serum, Therapeutic, Type 5** Ampuls containing 20 000 and 50 000 units respectively

**Antipneumococcic Rabbit Serum, Therapeutic, Type 7** Ampuls containing 20 000 and 50 000 units respectively

**Antipneumococcic Rabbit Serum, Therapeutic, Type 8** Ampuls containing 20 000 and 50 000 units respectively

**LEDERLE LABORATORIES, INC**

**Antipneumococcic Serum (Rabbit), Type 1** Vial 50 000 units A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 1 pneumococcus It contains 0.4 per cent phenol and 1/50 000 phenyl mercuric acetate as a preservative

**Antipneumococcic Serum (Rabbit), Type 2** Vial 50 000 units A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 2 pneumococcus It contains 0.4 per cent phenol and 1/50 000 phenyl mercuric acetate as a preservative

**Bivalent Antipneumococcic Serum, Refined and Concentrated** Vial containing 50 000 units of Type 1 and Type 2 packaged with vial of normal horse serum (1/10 dilution) for the conjunctival test

**Antipneumococcic Serum (Rabbit) Type 3** Vial 50 000 units Also available in vials containing 100 000 units Each package contains a vial of normal rabbit serum (1/10 dilution) for the conjunctival test A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 3 pneumococcus

It contains 0.4 per cent phenol and 1-50,000 phenyl mercuric acetate as a preservative.

**Antipneumococcic Serum (Rabbit), Type 4:** Vial, 50,000 units. A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 4 pneumococcus. It contains 0.4 per cent phenol and 1-50,000 phenyl mercuric acetate as a preservative.

**Antipneumococcic Serum (Rabbit), Type 5:** Vial, 50,000 units. A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 5 pneumococcus. It contains 0.4 per cent phenol and 1-50,000 phenyl mercuric acetate as a preservative.

**Antipneumococcic Serum (Rabbit), Type 7:** Vial, 50,000 units. A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 7 pneumococcus. It contains 0.4 per cent phenol and 1-50,000 phenyl mercuric acetate as a preservative.

**Antipneumococcic Serum (Rabbit), Type 8:** Vial, 50,000 units. A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 8 pneumococcus. It contains 0.4 per cent phenol and 1-50,000 phenyl mercuric acetate as a preservative.

**Antipneumococcic Serum (Rabbit), Type 14:** Vial, 50,000 units. A refined and concentrated globulin solution of pneumococcus antibodies prepared by immunizing rabbits against virulent cultures of the type 14 pneumococcus. It contains 0.4 per cent phenol and 1-50,000 phenyl mercuric acetate as a preservative.

### Naturally Produced Antibodies

In certain infectious diseases the etiological agent may be of such a nature as to make it impractical to produce a satisfactory immune serum in animals. In the absence of artificially produced antibodies, the best source of antibodies is from human beings who are convalescing from the specific infectious disease. During convalescence from an active infection an individual's serum usually contains antibodies against the specific infectious agent far in excess of the amount normally present. The amount of antibodies, however, is not as great as when animals are artificially immunized by the repeated injections of antigens. An outstanding attribute of naturally produced antibodies, or convalescent serums, is that their source is from a member of the same species, and thus there is less danger of a reaction to the protein of another species, but reaction may occur even with human serums.

**HUMAN MEASLES IMMUNE SERUM**—Measles Convalescent Serum—"Human Measles Immune Serum is sterile serum obtained from the bloods of healthy humans (*Homosapiens*) who have recently recovered from an attack of measles. It complies with the requirements of the National Institute of Health of the United States Public Health Service  
U S P

For description and standards see the U S Pharmacopeia under Serum Immune Morbillosi Humanum

*Actions and Uses*—Human measles immune serum is administered during the incubation period to prevent or modify the expected attack of measles

*Dosage*—To prevent the disease in infants and children of 6 years or under, 10 cc is given intramuscularly within five days after exposure. For children between 7 and 12 years of age, 15 cc is given, and for older children and adults 20 cc is given in like manner

Whether the serum is given for prevention or modification depends on the number of days the patient has been exposed. If prevention is desired, however, the dosage may have to be increased corresponding to the increase in days after exposure of the patient. If injection is made on the sixth or seventh day after exposure, a high percentage of patients have a modified type of measles which is followed by lasting immunity. It is probable that serum given after the seventh day following the initial exposure has little effect in either preventing or modifying the disease

The serum may be given either intravenously or intramuscularly. Vacuum dried serum should be given only intramuscularly

**MILWAUKEE CONVALESCENT SERUM CENTER, COLUMBIA HOSPITAL**

Measles Immune Serum (Human) 5 cc and 7.5 cc vials Preserved with merthiolate 1:10,000

**THE PHILADELPHIA SERUM EXCHANGE, THE CHILDREN'S HOSPITAL OF PHILADELPHIA**

Measles Immune Serum (Human) Containing sufficient amounts of frozen and dried serum to furnish 10 cc. and 20 cc of restored serum, packaged, respectively, with 10 cc. and 20 cc containers of sterile distilled water for dilution (preserved with 0.35 per cent of phenol)

**SAMUEL DEUTSCH CONVALESCENT SERUM CENTER, MICHAEL REESE HOSPITAL**

Human Convalescent Measles Serum 5 cc., 7.5 cc. and 20 cc vials Preserved with 0.3 per cent of tricresol

**HUMAN SCARLET FEVER IMMUNE SERUM.—**

Scarlet Fever Convalescent Serum—"Human Scarlet Fever Immune Serum is a sterile serum obtained from the blood of a healthy human (*Homo sapiens*) who has survived an attack of scarlet fever. It complies with the requirements of the National Institute of Health of the United States Public Health Service" *U S P*

For description and standards see the *U S Pharmacopoeia* under Serum Immune Scarlatinae Humanum

*Actions and Uses*—Human scarlet fever immune serum is of value in transferring passive immunity to a patient exposed to scarlet fever. The evidence as to therapeutic activity is conflicting. It may be used in patients sensitive to horse serum though the antitoxic content of convalescent serum is low. It does not seem wholly adequate to meet septic complications.

*Dosage*—For prophylaxis in infants and young children under 6 years of age, 10 cc amounts are given, for children between 6 and 12 years of age, 15 cc, and over 12 years of age and for adults 15 to 20 cc amounts are given, intramuscularly. If the individual is continuously exposed, it is recommended that a second dose be given ten days after the first injection.

**MILWAUKEE CONVALESCENT SERUM CENTER, COLUMBIA HOSPITAL**

Scarlet Fever Immune Serum (Human): 10 cc and 20 cc. vials. Preserved with 0.3 per cent of tricresol.

**THE PHILADELPHIA SERUM EXCHANGE, THE CHILDREN'S HOSPITAL OF PHILADELPHIA**

Scarlet Fever Immune Serum (Human): 10 cc., 15 cc and 20 cc vials, also containers having sufficient amounts of dried serum to yield 10 cc., 15 cc and 20 cc of restored serum, packaged with 10 cc ampuls of sterile distilled water for dilution. The diluent contains 0.35 per cent of phenol.

**SAMUEL DEUTSCH CONVALESCENT SERUM CENTER, MICHAEL REESE HOSPITAL**

Human Convalescent Scarlet Fever Serum: 10 cc and 20 cc vials. Preserved with 0.3 per cent of tricresol.

**VACCINES****(Agents for Producing Active Immunity)**

The use of substances for the production of active immunity has the following advantages over passive immunization (use of serums). (a) the antibodies are formed in the patient's own tissues and are not eliminated from the patient's system as rapidly as are antibodies which are contained in serum from another species; for example, the protection conferred by vaccination against smallpox lasts for years, while the prophylactic action of diphtheria antitoxin lasts only two or three weeks,

(b) not only are the immune mechanisms of the blood made available, but the fixed cells of the body may also take part in the immunization process, (c) an individual, who has been actively immunized by the administration of a vaccine, reacts more quickly and to a greater extent than a normal individual, or an individual previously passively immunized, on a subsequent encounter with the antigen. The second response may be against a subsequent dose of the vaccine or an exposure to the antigenic substance in nature.

On the other hand active immunization is not without its limitations. Considerable time, a matter of several days and even weeks, is required for active immunity to develop in an individual in response to the administration of a vaccine. Often it is necessary for the person to have immediate protection against a disease as in the case of a known exposure to the disease. Not all individuals respond to a vaccine, some acquiring a more effective resistance than others. A patient's body may already be overloaded with antigens, as the result of the disease and the introduction of additional antigens sufficient for an immune response in a normal individual, might in itself prove harmful to the patient.

Antigens may be of various sorts. The vaccine may be the living virus but in an attenuated form, as for example small pox vaccine, which is the living virus of smallpox attenuated by passage through the bovine species. The antigenic substances more commonly, are dead bacterial cells, as for example the extensively used typhoid vaccine. Not infrequently the antigenic substances are products of the bacterial cells such as the bacterial toxins. In recent times it has been found possible to destroy the toxic effect of bacterial toxins without destroying their ability to stimulate antibody production when introduced into the animal body. Examples of this are toxin antitoxin mixture and the various toxoids.

### Attenuated Living Viruses or Killed Viruses

**RABIES VACCINE** — Antirabic Vaccine — Antirabic Virus — Pasteur Treatment — Pasteur Prophylactic — An uncontaminated suspension of the attenuated diluted dried or dead fixed virus of rabies. The virus is obtained from the tissue of the central nervous system of an animal suffering from fixed virus rabies infection. It complies with the requirements of the National Institute of Health of the United States Public Health Service, U S P.

For description and standards see the U S Pharmacopeia under *Vaccinum Rabies*.

**Actions and Uses** — By treatment with rabies vaccine after the bite of a rabid animal immunity is often established before the incubation period of the disease is completed and rabies is thus prevented. The treatment fails not infrequently and in a small percentage of cases it is followed by paralysis which is usually transient but rarely may be permanent or even fatal.

**RABIES VACCINE (CUMMING).**—The vaccine is prepared by dialyzing a 1 per cent suspension of brain tissues from a rabbit dying of rabies (induced by an infection of fixed virus) against running water until the active, virulent virus is destroyed.

*Actions, Uses and Dosage.*—When employed for the prophylaxis of rabies, the treatment is divided into two classes: mild, requiring 14 doses; severe, requiring 21 doses. One dose, 2 cc., is given daily over a period of either 14 or 21 days.

Brains and spinal  
 sis, following infec-  
 frozen with carbon  
 The resulting dry  
 ised by Dr. Harris  
 and stored in *vacuo* in the cold. One dose is given daily over  
 a period of 10 days or more, doses increasing in unitage up to  
 a maximum.

#### DR. D. L. HARRIS LABORATORY

**Rabies Vaccine (Harris):** Vacuum sealed tubes packaged in series of ten consecutive doses of increasing potency, with ten vials of physiological solution of sodium chloride to prepare the vaccine suspension, and a Luer syringe with needle.

#### ELI LILLY AND COMPANY

**Rabies Vaccine (Harris):** 0.5 cc. vials, packaged in series of fourteen consecutive doses of increasing potency, with a special syringe unit.

**RABIES VACCINE (PASTEUR)—(PASTEUR ANTIRABIC VACCINE).**—The virus is prepared in accordance with the general method of the U. S. Public Health Service. One-fifth of an inch of dried cord, emulsified in 0.6 cc. of 60 per cent glycerin containing 0.3 per cent tricresol is supplied.

*Actions and Uses.*—Rabies vaccine (Pasteur) is employed for the prophylaxis of rabies.

*Dosage.*—Prophylactic treatment consists of twenty-one doses which are administered at twenty-four hour intervals, and these are sent in three installments of seven doses each. The installments are sent by special delivery mail. The first dose consists of two sections of a cord dried for six days, the second dose consists of two sections of a cord dried for five days, and the third dose two sections of a cord dried for four days. The remaining eighteen doses are prepared from single sections of cords dried as follows: 3, 3, 2, 2, 1, 5, 4, 4, 3, 3, 2, 2, 4, 3, 2, 3, 2, 1 days. They are administered in the order listed. Each dose of the dried cord is diluted with 2.5 cc. of sterile sodium chloride solution in the syringe at the time of injection.

**RABIES VACCINE (SEMPLÉ)**—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains or brains and spinal cords of rabbits killed on about the sixth day after inoculation with the fixed virus of rabies are triturated with physiological solution of sodium chloride containing 1 per cent phenol. The mixture is strained, incubated at 37° C for (usually) 24 hours and then diluted with an equal volume of physiological solution of sodium chloride, so that the finished product contains a definite amount of brain substance and about 0.5 per cent phenol. Put up in containers each containing usually sufficient material for a daily dose.

*Actions and Uses*—Rabies vaccine (Semple) is used in the prophylactic treatment of rabies.

*Dosage*—0.5 cc, 1 cc, 2 cc or 3 cc of the suspended vaccine (depending on the dilution employed) daily over a period of from seven to twenty-eight days depending on the site and severity of the injury. The potency of each dose is approximately the same irrespective of the volume of the suspension in which it is supplied.

#### **CUTTER LABORATORIES**

**Rabies Vaccine (Semple)** 1 cc vials packaged in units of seven vials. Preserved with 0.5 per cent of phenol.

#### **THE GILILAND LABORATORIES, INC.**

**Rabies Vaccine (Semple Method)** 2 cc vials and 2 cc syringes each packaged in units of fourteen vials or syringes respectively. Preserved with 0.5 per cent of phenol.

**Rabies Vaccine (Modified Semple Method)** 0.5 cc vials packaged in units of seven and fourteen vials. Preserved with 0.5 per cent of phenol.

#### **JENSON SALSBERG LABORATORIES, INC.**

**Rabies Vaccine (Killed Virus)** Vials containing 12.5 per cent of brain and cord substance packaged in units of seven vials. Preserved with 0.5 per cent of phenol.

#### **LLDENLE LABORATORIES, INC.**

**Rabies Vaccine (Semple Method)** 2 cc vials packaged in units of seven and fourteen vials. Preserved with 0.45 per cent of phenol.

#### **MEDICAL ARTS LABORATORY, INC.**

**Rabies Vaccine (Killed Virus)** 2 cc vials packaged in units of seven and fourteen vials. Preserved with 0.5 per cent of phenol.



**THE NATIONAL DRUG CO**

**Rabies Vaccine Human (Phenol Killed):** 0.5 cc vials in packages of seven, without syringe, and packages of fourteen with syringe. Preserved with 0.5 per cent of phenol.

**PITMAN-MOORE COMPANY**

**Rabies Vaccine (Killed Virus) Semple Method:** 1 cc. vials packaged in units of seven vials. Preserved with 0.25 per cent of phenol and merthiolate 1 to 20,000.

**SHARP & DOHME, INC**

**Rabies Vaccine (Phenol Killed):** 0.5 cc vials packaged in units of seven vials without syringe, and in units of fourteen vials with or without syringe.

**E. R. SQUIBB & SONS**

**Rabies Vaccine (Semple Method):** 2 cc vials packaged in units of fourteen vials with syringe and needles. Also packaged in units of seven vials, each containing 2 cc. Preserved with 0.5 per cent of phenol.

**TERRELL'S LABORATORIES**

**Rabies Vaccine (Phenolized):** 3 cc vials packaged in units of fourteen and twenty-one vials. Preserved with 0.5 per cent of phenol.

**U. S. STANDARD PRODUCTS CO.**

**Rabies Vaccine (Semple):** 0.5 cc vials packaged in units of seven and fourteen vials, 1 cc vials packaged in units of fourteen vials, 2 cc vials and 2 cc syringes each packaged in units of seven and fourteen vials or syringes, and the latter in units of twenty-one syringes. Preserved with 0.5 per cent of phenol.

**RABIES VACCINE, CHLOROFORM KILLED.—**

Antirabic vaccine prepared according to a modification of the method of David Semple in which the virus is killed with chloroform instead of phenol. The brains and spinal cords of rabbits killed on the sixth or seventh day after inoculation with fixed rabies virus are ground with solution of sodium chloride containing 2 per cent chloroform, to yield a 25 per cent suspension of brain and cord substance. The suspension is then placed in the refrigerator at 2 to 5 C. for two months. It is then tested for absence of living virus by rabbit injection. The finished product represents a 25 per cent emulsion.

*Actions, Uses and Dosage*—Same as Rabies Vaccine (Semple)

**THE GILLIAND LABORATORIES, INC.**

**Rabies Vaccine (Chloroform Killed Virus):** 0.5 cc. vials packaged in units of seven and fourteen vials.

## THE NATIONAL DRUG CO.

**Rabies Vaccine (Chloroform Killed):** 0.5 cc vials packaged in units of seven and 0.5 cc vials packaged in units of fourteen vials with syringes

## Bacterial Toxins

Bacterial toxins are sterile solutions obtained by filtering fluid cultures of the microorganisms through bacteria excluding filters. The filtrate of toxin contains, in addition to the true bacterisms, their cells, and the unused portions of the culture medium.

**SCARLET FEVER STREPTOCOCCUS TOXIN—**Scarlet Fever Streptococcus Toxin—Scarlet Fever Toxin for Immunization and for the Dick Test—Scarlet Fever Streptococcus Toxin is a sterile solution in a medium containing not more than 1 per cent of peptone but no meat extractive, of certain products including a soluble toxin, resulting from the growth in the broth of suitable strains of hemolytic streptococci (*Streptococcus scarlatinae*). It complies with the requirements of the National Institute of Health of the United States Public Health Service" U S P

For description and standards see the U S Pharmacopoeia under Toxinum Scarlatinae Streptococcicum

For diagnostic scarlet fever preparations see under Diagnostic Agents

**Actions, Uses and Dosage**—The toxin is used for active immunization. For this purpose it is injected subcutaneously at weekly intervals. The amount of toxin necessary for immunity production varies with the individual. Five to six doses are given, beginning with 162 to 650 skin test doses for the first injection and increasing the amount of toxin in each subsequent injection to a final dose of 100,000 to 120,000 skin test doses. Immunity to the toxin appears in a few weeks and is determined by the absence of a reaction to the intracutaneous test.

## LEDLER LABORATORIES, INC

**Scarlet Fever Streptococcus Immunizing Toxin** 1 cc and 10 cc vials (single and ten immunization doses respectively), each packaged in units of five vials containing respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter, also the 1 cc vial containing 100,000-120,000 skin test doses is packaged separately.

## THE NATIONAL DRUG CO

**Scarlet Fever Streptococcus Toxin for Immunization** 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test

doses per cubic centimeter (1 cc vial containing 100,000-120,000 skin test doses is also packaged separately); 10 cc. vials packaged in units of six vials containing, respectively, 650, 2,500, 10,000, 30,000, 100,000-120,000 and 100,000-120,000 skin test doses per cubic centimeter

#### PARKE, DAVIS & COMPANY

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; 10 cc vials packaged in units of six vials containing, respectively, 650, 2,500, 10,000, 30,000, 100,000-120,000 and 100,000-120,000 skin test doses per cubic centimeter.

#### SHARP & DOHME, INC.

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. and 10 cc ampul-vials (single and ten immunization doses respectively), each packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; the 1 cc vial containing 100,000-120,000 skin test doses is also packaged separately

#### E. R. SQUIBB & SONS

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter, 10 cc. vials packaged in units of six vials containing, respectively, 650, 2,500, 10,000, 30,000, 100,000-120,000 and 100,000-120,000 skin test doses per cubic centimeter and in single vial packages containing 100,000-120,000 skin test doses. Preserved with 0.5 per cent of phenol and buffered with  $\text{KH}_2\text{PO}_4$  and  $\text{NaOH}$ .

#### U. S. STANDARD PRODUCTS Co.

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; 10 cc. vials packaged in units of six vials containing, respectively, 650, 2,500, 10,000, 30,000, 100,000-120,000 and 100,000-120,000 skin test doses per cubic centimeter.

### Bacterial Toxins, Modified

Certain bacterial toxins may be modified so as to retain their capacity for bringing about an immune response while at the same time they are made relatively harmless, or at least their toxicity is greatly decreased. Examples of such modified bacterial toxins are Diphtheria Toxin-Antitoxin Mixture and Diphtheria Toxoid

*Toxin Antitoxin Mixture***DIPHTHERIA TOXIN-ANTITOXIN MIXTURE.**—

*Mistura Toxini Diphtherici et Antitoxini Diphtherici*—A mixture of diphtheria toxin and diphtheria antitoxin. Labelled to show the volume of each dose and the amount of L+ doses of toxin contained in each dose. Each 1 cc represents 0.1 L+ dose of diphtheria toxin neutralized with a proper amount of diphtheria antitoxin.

The product should be used only if clear and free from sediment or flocculi.

The antitoxin used in diphtheria toxin antitoxin mixture is produced from the horse, goat or sheep. Diphtheria toxin antitoxin mixture has been largely supplanted by diphtheria toxoid.

*Actions, Uses and Dosage*—Diphtheria toxin antitoxin mixture is used for active immunization against diphtheria. It is employed chiefly for those who react severely to toxoid, principally older children and adults, ordinarily diphtheria toxoid is preferred. It is administered subcutaneously, preferably at the insertion of the deltoid in three doses with an interval of one week between doses. A Schick test performed about six months after the last injection determines whether further immunization is necessary. In the presence of an outbreak of diphtheria an immunizing dose of diphtheria antitoxin alone should be used if exposed children cannot be kept under regular medical observation.

**THE GILLILAND LABORATORIES, INC.**

Ampuls Diphtheria Toxin-Antitoxin Mixture 1 cc  
10 cc 20 cc and 30 cc

Diphtheria Toxin Antitoxin Mixture 1 cc syringe

Diphtheria Toxin Antitoxin Mixture (Goat) 1 cc  
10 cc 20 cc and 30 cc vials

**THE NATIONAL DRUG CO.**

Diphtheria Toxin Antitoxin Mixture 1 cc 10 cc 15 cc  
and 30 cc vials

**PADKE, DAVIS & COMPANY**

Diphtheria Toxin Antitoxin Mixture (Goat) 1 cc bulb  
and 30 cc vial

*Toxoids*

**DIPHTHERIA TOXOID**—Anatoxin Ramon—Diphtheria Anatoxin.—A sterile aqueous solution of the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity. The toxicity of the Diphtheria Toxoid shall be so low that five times the dose for

the adult human does not cause either local or general symptoms of diphtheria poisoning in a guinea pig within thirty days after its injection into the animal. The antigenic value shall be such that the initial dose for the human shall protect at least 80 per cent of guinea pigs, six weeks after injection, against five minimum lethal doses each of diphtheria test toxin. Diphtheria Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service "U. S. P."

For description and standards see the U. S. Pharmacopeia under *Toxoidum Diphthericum*.

**Actions, Uses and Dosage** — Diphtheria toxoid is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid, in two or three doses of 1 cc. each with an interval of three or four weeks between doses. Since some local and general reactions have been observed in adults and in children over 8 years of age, an intracutaneous test dose of 0.1 cc. of the toxoid diluted (1 in 20) with physiological saline solution should be given to determine sensitivity in such persons.

#### CUTLER LABORATORIES

Diphtheria Toxoid: 1 cc., 10 cc. and 30 cc. vials in packages of two and of 20 1 cc. vials, one 10 cc. vial and one 30 cc. vial. Preserved with 1:10,000 merthiolate.

#### THE GILLILAND LABORATORIES, INC.

Diphtheria Toxoid: 1 cc. and 30 cc. vials in packages of two and of twenty 1 cc. vials, and one 30 cc. vial. Each package is accompanied by a sufficient amount of diluted diphtheria toxoid for the reaction test.

#### LEDERLE LABORATORIES, INC.

Diphtheria Toxoid: 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Each package is accompanied by a vial containing sufficient diluted diphtheria toxoid for ten sensitivity tests.

#### ELI LILLY AND COMPANY

Diphtheria Toxoid: 1 cc. and 30 cc. vials in packages of two 1 cc. vials, and one 30 cc. vial. Preserved with 1:10,000 merthiolate.

#### THE NATIONAL DRUG CO.

Diphtheria Toxoid (Plain): 1 cc. vials in packages of two 1 cc. vials, 3 cc. and 15 cc. ampule-vials. Preserved with 1:10,000 merthiolate.

#### PARKE, DAVIS & COMPANY

Diphtheria Toxoid: 0.5 cc. and 1 cc. bulbs and 30 cc. vials in packages containing one 0.5 cc. bulb and one 1 cc. bulb, and one 30 cc. vial.

**SHARP & DOHME, INC**

**Diphtheria Toxoid** 1 cc and 30 cc vials in packages of two and of twenty 1 cc vials and one 30 cc vial

**E R SQUIBB & SONS**

**Ampuls Diphtheria Toxoid** 1 cc in packages of three ampuls with a 1 cc vial of diluted diphtheria toxoid for the reaction test Preserved with 1 10 000 merthiolate

**Diphtheria Toxoid** 30 cc vial in single packages with a 1 cc vial of diluted diphtheria toxoid for the reaction test. Preserved with 1 10 000 merthiolate

**U S STANDARD PRODUCTS CO**

**Diphtheria Toxoid.** 1 cc, 60 cc, 20 cc and 30 cc vials in packages of two 1 cc vials one 6 cc vial, one 20 cc vial and one 30 cc vial

**DIPHTHERIA TOXOID, ALUM PRECIPITATED**

—Refined Diphtheria Toxoid A turbid white, slightly gray or slightly pink suspension prepared by adding a sterile aqueous solution of alum to Diphtheria Toxoid washing the resultant precipitate with isotonic solution of sodium chloride, and resuspending it in isotonic solution of sodium chloride to which a suitable preservative may be added *U S P*

For description and standards see the *U S Pharmacopeia* under *Toxoidum Diphthericum*

*Actions Uses and Dosage*—Diphtheria toxoid alum precipitated is used for active immunization against diphtheria. It is administered subcutaneously preferably at the insertion of the deltoid muscle. Because of the physical character of the product, absorption is delayed. Two doses or more of 0.5 cc. (or 1 cc if this amount is necessary to furnish two units of antitoxin) with an interval of 4 to 6 weeks are advisable to obtain a reversal of the Schick reaction although a single dose sometimes is sufficient. A nodule persists at the site of inoculation for several days and rarely an abscess forms.

**CUTTER LABORATORIES**

**Diphtheria Toxoid, Alum Precipitated, Refined** 1 cc and 10 cc vials Preserved with 1 10 000 merthiolate.

**THE GILLILAND LABORATORIES, INC**

**Diphtheria Toxoid, Alum Precipitated (Refined)** 0.5 cc, 1 cc, 5 cc and 10 cc vials in packages of one and of ten 0.5 cc vials one and ten 1 cc vials, one 5 cc vial and one 10 cc vial Preserved with 1 10 000 merthiolate

**LEDERLE LABORATORIES, INC**

**Refined Diphtheria Toxoid, Alum Precipitated** 0.5 cc 1 cc 5 cc and 10 cc vials 10 packages of two 0.5 cc vials

two 1 cc vials, one 5 cc vial and one 10 cc vial Preserved with 1:10,000 merthiolate

#### ELI LILLY AND COMPANY

**Diphtheria Toxoid, Alum Precipitated:** 0.5 cc and 5 cc vials

#### THE NATIONAL DRUG CO.

**Refined Diphtheria Toxoid (Alum Precipitated).** 0.5 cc and 5 cc vials, also in 10 cc vial representing five immunizations For the two dose immunization treatment, one 2 cc vial and two 10 cc vials representing respectively one and ten immunizations Preserved with merthiolate 1:10,000

#### PARKE, DAVIS & COMPANY

**Diphtheria Toxoid, Alum Precipitated (Refined):** 0.5 cc and 5 cc vials containing one and ten doses, respectively, 1 cc and 10 cc vials containing one and ten doses, respectively. Preserved with 1:10,000 merthiolate

#### PITMAN-MOORE COMPANY

**Diphtheria Toxoid (Alum Precipitated, Refined):** Two 1 cc vials (2 doses), and 10 cc vials (10 doses) Preserved with 1:10,000 merthiolate

#### SHARP & DOHME, INC.

**Diphtheria Toxoid, Alum Precipitated, Refined:** 0.5 cc, 1 cc, 5 cc and 10 cc vials in packages of one 0.5 cc vial and one 1 cc vial, and of one 5 cc vial and one 10 cc vial Preserved with 1:20,000 ortho chloromercuri phenol

#### E. H. SQUIBB & SONS

**Refined Diphtheria Toxoid, Alum Precipitated** 1 cc vial in packages of two vials and 10 cc vials Preserved with 1:10,000 merthiolate

#### U. S. STANDARD PRODUCTS CO.

**Diphtheria Toxoid, Alum Precipitated, Refined:** 1 cc and 10 cc vials in packages of one and of ten 1 cc vials, and one 10 cc vial Preserved with 1:10,000 merthiolate

**DIPHTHERIA TOXOID, TETANUS TOXOID, ALUM PRECIPITATED, COMBINED.**—Combined diphtheria toxoid and tetanus toxoid, alum precipitated

*Actions, Uses and Dosage.*—Same as for Diphtheria Toxoid and Tetanus Toxoid, Alum Precipitated (Refined), except that single doses are generally 1 cc in volume

#### ELI LILLY AND COMPANY

**Combined Diphtheria Toxoid-Tetanus Toxoid, Alum Precipitated.** 1 cc and 10 cc vials in packages of two 1 cc vials and of one 10 cc vial

**STAPHYLOCOCCUS TOXOID**—*Staphylococcus* Antitoxin—Univalent or polyvalent, potently hemolytic and dermonecrotic toxins of *Staphylococcus aureus* and *albus* altered by the formaldehyde detoxifying process of Burnett (modified from Ramon). Antigenuity is maintained but toxicity is greatly diminished. The antigenic potency is determined by injecting 1 cc of toxoid per kilogram intravenously into three rabbits and the resulting serum tested at the end of one and two weeks for its content of staphylococcus antitoxin. No staphylococcus toxoid is used which in doses of 0.2 cc or less of the undiluted material will cause necrosis when injected into rabbits. The toxin is titrated to determine its dermonecrotic potency.

**Actions, Uses and Dosage**—*Staphylococcus* toxoid has been reported a valuable agent in the prophylaxis and therapy of various staphylococcal pyodermas and localized pyogenic processes due to *Staphylococcus aureus* and *albus* (boil, carbuncle, furunculosis, acne, and so on). The toxoid is said to be effective in producing active immunity to the dermonecrotic and hemolytic elements of the toxins of *Staphylococcus aureus* and *albus* irrespective of the individual strain of the infecting organism. The toxoid induces the production of staphylococcus antitoxin in the blood serum of immunized persons.

The initial dose should be not more than 0.1 cc containing 10 skin necrotizing doses, injected subcutaneously at the insertion of the deltoid. Subsequent doses at weekly intervals should be increased by 10 to 20 skin necrotizing doses. Marked local or a systemic reaction to any dose contraindicates increase of the succeeding dose.

#### LEDERLE LABORATORIES, INC.

**Staphylococcus Toxoid**. 5 cc vials containing in each cubic centimeter the toxoid derived from 100 and 1 000 necrotizing doses of toxin respectively. Preserved with 1:10 000 merthiolate.

#### THE NATIONAL DRUG CO.

**Staphylococcus Toxoid**. 5 cc vials containing in each cubic centimeter the toxoid derived from 100 and 1 000 necrotizing doses of toxin respectively.

#### PANKE, DAVIS & COMPANY

**Staphylococcus Toxoid**. 5 cc vials containing in each cubic centimeter the toxoid derived from 100 and 1 000 necrotizing doses of toxin respectively. Preserved with 1:10 000 merthiolate.

#### PITMAN-MOORE COMPANY

**Staphylococcus Toxoid**. 5 cc vials containing in each cubic centimeter the toxoid derived from one necrotizing dose of toxin. Preserved with 1:10 000 merthiolate.



SHARP & DOHME, INC.

**Staphylococcus Toxoid:** 5 cc vials containing in each cubic centimeter the toxoid derived from 100 and 1,000 necrotizing doses of toxin, respectively

E. R. SQUIBB & SONS

**Staphylococcus Toxoid:** 5 cc vial containing in each cubic centimeter the toxoid derived from 1,000 necrotizing doses of toxin Preserved with 1:10,000 merthiolate

**TETANUS TOXOID.**—Tetanus Toxoid is a sterile solution of the product of growth of the tetanus bacillus (*Clostridium tetani*) so modified by treatment with solution of formaldehyde as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity

The toxicity of Tetanus Toxoid shall be so low that 5 cc. of the material does not cause any symptoms of tetanus in a guinea pig within a period of twenty-one days after its injection into the animal The antigenic value shall be such that 1 cc of the material six weeks after injection shall protect at least 80 per cent of guinea pigs from all symptoms of tetanus for a period of ten days after the injection of 10 minimum lethal doses of tetanus test toxin into each animal

**Actions, Uses and Dosage.**—To protect against infection, three doses of 1 cc each intramuscularly or subcutaneously with an interval of three weeks between injections An additional dose of 1 cc. should be given at the time of injury or infection

LEDERLE LABORATORIES, INC

**Tetanus Toxoid (Fluid):** 1 cc and 30 cc vials in packages of three 1 cc. vials and one 30 cc. vial

PITMAN-MOORE COMPANY

**Tetanus Toxoid (Alum Precipitated):** 1 cc vials in packages of two 1 cc vials (two immunizing doses) and 10 cc vial (ten immunizing doses)

E. R. SQUIBB & SONS

**Tetanus Toxoid:** 1 cc, 3 cc and 30 cc. rubber diaphragm capped vials

**TETANUS TOXOID, ALUM PRECIPITATED.**—Refined Tetanus Toxoid—"Alum Precipitated Tetanus Toxoid is a turbid white or slightly gray suspension prepared by adding a sterile aqueous solution of alum to Tetanus Toxoid, washing the resultant precipitate with isotonic solution of sodium chloride, and resuspending it in isotonic solution of sodium chloride to which a suitable preservative may be added" U. S. P

For description and standards see the U. S. Pharmacopeia under *Toxoidum Tetanicum*

*Actions, Uses and Dosage*—Tetanus toxoid is recommended for the production of active immunity to tetanus. The recommended human dose (10 cc or 0.5 cc) is injected subcutaneously, preferably in the region of the deltoid. Approximately three months later the second and final injection is given. The immunity thus produced is reasonably persistent. However it has been shown that if some time after the original immunization a single injection of toxoid is given, there results a prompt (within two weeks) and marked rise in the antitoxic titer of the serum. Thus in cases of injury to persons previously immunized an injection of tetanus toxoid may suffice to protect against tetanus in place of the usual tetanus antitoxin. It should be borne in mind that in these cases several weeks is required, following the second injection of toxoid, before immunity may be assumed to be well established. Therefore in any dubious instance the conservative course is the administration of antitoxin. Active immunization to tetanus would appear to be a desirable procedure in the case of individuals who are subject to a greater than normal hazard of the disease.

#### **THE GILLILAND LABORATORIES, INC**

Tetanus Toxoid, Alum Precipitated (Refined) 0.5 cc and 1 cc vials in packages of two 0.5 cc vials (two immunizing doses) and of two 1 cc vials (two immunizing doses), 5 cc vial (ten immunizing doses) and 10 cc vial (ten immunizing doses)

#### **FEDERLE LABORATORIES, INC**

Refined Alum Precipitated Tetanus Toxoid 1 cc and 10 cc vials in packages of two 1 cc vials (two immunizing doses), and of one 10 cc vial (ten immunizing doses)

#### **ELI LILLY AND COMPANY**

Tetanus Toxoid, Alum Precipitated 0.5 cc and 5 cc vials in packages of two 0.5 cc vials (two immunizing doses) and of one 5 cc vial (ten immunizing doses)

#### **THE NATIONAL DRUG CO**

Refined Tetanus Toxoid (Alum Precipitated) 1 cc and 10 cc vials in packages of two 1 cc vials (two immunizing doses) and of one 10 cc vial (ten immunizing doses) packages of 1 cc vials for supplementary dosage

#### **PANKE, DAVIS & COMPANY**

Tetanus Toxoid, Alum Precipitated (Refined) Two 1 cc vials (one immunization treatment) and one 10 cc vial (five immunization treatments)

#### **SHARP & DOHME, INC**

Tetanus Toxoid, Alum Precipitated, Refined 1 cc and 10 cc vials in packages of two 1 cc vials (two immunizing doses) and of one 10 cc vial (ten immunizing doses) also packages of 1 cc vials for supplementary dosage

## E. R. SQUIBB &amp; SONS

**Refined Tetanus Toxoid, Alum Precipitated:** 1 cc. vials in packages of two each (two immunizing doses); 10 cc. vials (ten immunizing doses). Preserved with 1/10,000 merthiolate

**Bacterial Vaccines**

Bacterial vaccines, or bacterins, are suspensions of killed bacteria in physiological solution of sodium chloride, usually with the addition of some preservative such as cresol or phenol.

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely. In general, the severer the disease, the smaller the dose should be; and the smaller the doses, the shorter the intervals. In mild affections no improvement may result until the vaccine is pushed to a systemic reaction.

Prophylactically, the typhoid and paratyphoid vaccines apparently have proved of great value as compared to other stock bacterial vaccines, the therapeutic use of which often rests on uncertain clinical evidence. Plague and cholera vaccines are also used in prophylaxis.

**BACTERIAL VACCINE MADE FROM THE ACNE BACILLUS (Acne Bacillus Vaccine).—**Prepared from the acne bacillus of Unna and Sabouraud, *Corynebacterium acnes*

**Actions and Uses.**—The acne bacillus is not found in all cases of acne; but in those cases in which the bacillus is found (*acne vulgaris*) it seems to be the active pathogenic agent and the use of acne vaccine may give good results, especially in the cystic form and in acne indurata. In other cases, *staphylococci* are responsible for the inflammation, and the corresponding staphylococcus vaccine or toxoid may be tried.

**Dosage.**—5 to 50 million killed bacteria

**CUTTER LABORATORIES**

**Acne Bacillus Vaccine.** 5 cc. vial. Each 1 cc. contains 100 million killed acne bacilli suspended in physiological solution of sodium chloride. Preserved with 0.5 per cent phenol.

**BACTERIAL VACCINE MADE FROM BRUCELLA (Undulant Fever Vaccine).—**A bacterial vaccine obtained from *Brucella melitensis*, *Br. abortus* or *Br. suis*. No potency tests are made. Purity of cultures is determined by the study of colony formation, carbohydrate reactions and agglutination test with specific serum.

**Actions and Uses.**—Undulant fever vaccine is proposed for use in the treatment of undulant fever.

**Dosage.**—Subcutaneously or intramuscularly, 0.1 cc. to 0.25 cc. of the vaccine containing 2 to 6 billion killed organisms is used for the initial dose. Subsequent doses are gradually increased.

by the amount of the initial dose and may be administered at two to five day intervals until a dose of 1 cc is reached. This amount is then repeated at the same intervals for a total of seven injections.

#### JENSEN SALSBERG LABORATORIES, INC

**Undulant Fever Bacterial Vaccine** 1 cc vial. Each 1 cc contains 3 billion each of killed *Br abortus* and *Br suis* in physiological solution of sodium chloride preserved with 0.5 per cent of phenol.

#### LEDERLE LABORATORIES, INC

**Undulant Fever Vaccine** 5 cc vial. Each 1 cc contains 1 000 million each of killed *Br abortus* and *Br suis*, in isotonic solution of sodium chloride preserved with 0.5 per cent of phenol.

#### THE NATIONAL DRUG CO

**Undulant Fever Vaccine (*Abortus* and *Suis*)** 5 cc and 30 cc vials. Each 1 cc contains 2 500 million each of killed *Br abortus* (bovine) and *Br suis* (porcine) preserved with 1:10 000 merthiolate.

**Undulant Fever Vaccine (*Melitensis*)** 5 cc and 30 cc vials. Each 1 cc contains 2 500 million killed *Br melitensis* (caprine) preserved with 1:10 000 merthiolate.

**BACTERIAL VACCINE MADE FROM THE CHOLERA VIBRIO (Cholera Vaccine)**—Prepared from killed cholera vibrios *Vibrio comma* (*cholerae*).

**Actions, Uses and Dosage**—This vaccine has been used for the prevention of cholera administered in three doses containing 500 million, 1 000 million and 1 000 million killed cholera vibrios respectively. The value of this vaccine has not been conclusively established.

**BACTERIAL VACCINE MADE FROM THE PLAGUE BACILLUS (Plague Bacillus Vaccine)**—Prepared from killed *Pasteurella pestis*.

**Actions, Uses and Dosage**—This vaccine has been used for the prevention of plague administered in two doses containing 1 000 million and 2 000 million killed bacilli respectively. The value of this vaccine is very doubtful.

**VACCINE MADE FROM STAPHYLOCOCCUS**—**Vaccinum** *Staphylococcus aureus* from *Staphylococcus albus* or from *Staphylococcus citreus* or from all three.

**Actions and Uses**—*Staphylococcus* vaccine is used in carbuncles, furunculosis, sycosis and certain cases of acne. An

autogenous vaccine is preferable, but if this cannot be made, a stock vaccine can be used with some prospect of success. The forms of acne most likely to respond are characterized by deep-seated pustules, with considerable induration, occurring on the face, chest and back. When the lesions are superficial and indolent, the acne bacillus vaccine may give good results.

*Dosage*—100 million to 1,000 million killed bacteria

#### ABBOTT LABORATORIES

**Staphylococcus Combined Vaccine:** 6 cc and 20 cc vials. Each 1 cc. contains 1,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*.

#### CUTTER LABORATORIES

**Staphylococcus Vaccine:** 5 cc vial. Each 1 cc contains 2,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*, in physiological solution of sodium chloride, preserved with 0.5 per cent of phenol.

#### THE GILLILAND LABORATORIES, INC.

**Staphylococcus Vaccine (*Albus* and *Aureus*):** 5 cc and 10 cc. vials. Each 1 cc contains 1,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*, in physiological solution of sodium chloride, preserved with 0.25 per cent of tricresol.

#### LEDERLE LABORATORIES, INC.

**Staphylococcus Aureus Vaccine:** 5 cc vial. Each 1 cc contains 2,000 million killed *Staphylococcus aureus*.

#### ELI LILLY AND COMPANY

**Staphylococcus Vaccine:** 5 cc and 20 cc vials. Each 1 cc. contains 2,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*, in physiological solution of sodium chloride, preserved with 1:10,000 merthiolate.

**Staphylococcus Aureus Vaccine:** 5 cc. and 20 cc. vials. Each 1 cc. contains 2,000 million killed *Staphylococcus aureus*. Preserved with 1:10,000 merthiolate.

#### THE NATIONAL DRUG CO.

**Staphylococcus Vaccine.** 5 cc. and 30 cc vials. Each 1 cc. contains 1,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*, in physiological solution of sodium chloride, preserved with 1:10,000 merthiolate.

#### PARKE, DAVIS & COMPANY

**Furunculosis Vaccine:** 1 cc, 5 cc and 20 cc bulbs. Each 1 cc. contains 2,000 million killed *Staphylococcus aureus*.

**Staphylococcus Vaccine (Combined)** 1 cc 5 cc. and 20 cc bulbs Each 1 cc contains 1 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*

#### THE UPJOHN COMPANY

**Staphylococcus Mixed Vaccine** 5 cc and 20 cc vials Each 1 cc contains 1 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus* in physiological solution of sodium chloride preserved with 0.5 per cent of phenol

**BACTERIAL VACCINE MADE FROM THE TYPHOID BACILLUS**—Typhoid Prophylactic—Enteric Vaccine—Typhoid Vaccine—A sterile suspension of killed typhoid bacilli (*Eberthella typhosa*) of a strain selected for high antigenic efficiency in isotonic solution of sodium chloride or other suitable diluent. The vaccine shall contain in each cc at least 1 000 000 000 typhoid organisms. It complies with the requirements of the National Institute of Health of the United States Public Health Service *U S P*

For description and standards see the *U S Pharmacopeia* under *Vaccinum Typhosum*

**Actions and Uses**—Typhoid vaccine is of considerable value in the prevention of typhoid fever. Typhoid vaccine is also used in nonspecific protein therapy but such use is sometimes attended by dangerous and even fatal reactions

**Dosage**—Average Dose—Hypodermic for active immunization 0.5 cc and 1 cc the latter dose to be repeated once.—*U S P* As a preventive typhoid vaccine should be administered only to healthy persons. The skin should be sterilized with iodine and an initial dose of 500 million bacteria injected with aseptic precautions. This injection should be followed in from seven to ten days by a second dose of one billion bacteria and a third injection of the same size is given from seven to ten days after the second

#### CUTTER LABORATORIES

**Typhoid Prophylactic** 1 cc bottles in packages of three one containing 500 million and two each containing 1 000 million killed bacilli (strain 58 the Panama carrier strain), 20 cc bottles containing 1 000 million killed bacilli of the same strain per cubic centimeter. Preserved with 0.25 per cent tricresol

#### THE GILLILAND LABORATORIES INC

**Typhoid Vaccine** 1 cc vials in packages of three one containing 500 million and two each containing 1 000 million killed bacilli (Rawlings strain or the Panama carrier strain as ordered) and in packages of thirty ten containing 500 million each and twenty containing 1 000 million each of either strain as desired. 5 cc 10 cc and 20 cc vials as ordered. 50 cc vials containing 1 000 million killed bacilli of either strain per cubic centimeter

## LEDERLE LABORATORIES, INC.

**Typhoid Vaccine (Prophylactic):** 5 cc. vial Each 1 cc contains 1,000 million killed bacilli (strain 58, the Panama carrier strain).

## ELI LILLY AND COMPANY

**Typhoid Vaccine, Prophylactic:** 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain) and in packages of ten, each containing 500 million or 1,000 million killed bacilli of the same strain Preserved with 1:10,000 merthiolate.

## THE NATIONAL DRUG CO.

**Typhoid Vaccine:** 1 cc. vials in packages of three, one containing 1,000 million and two each containing 2,000 million killed bacilli (strain 58, the Panama carrier strain); 5 cc, 15 cc and 30 cc. vials containing 2,000 million killed bacilli of the same strain per cubic centimeter. Preserved with 1:10,000 merthiolate.

## PARKE, DAVIS &amp; COMPANY

**Ampuls Typhoid Vaccine (Prophylactic):** 1 cc in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (Rawling's strain and the Panama strain in equal proportions).

**Typhoid Vaccine (Prophylactic):** 25 cc vials, in packages of ten, and 20 cc. vials containing 1,000 million killed bacilli (Rawling's strain and the Panama strain in equal proportions) per cubic centimeter

## E. R. SQUIBB &amp; SONS

**Ampuls Typhoid Vaccine (Immunizing):** 1 cc. in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain) and in packages of thirty, ten containing 500 million each and twenty containing 1,000 million each of killed bacilli of the same strain. Preserved with 0.5 per cent of phenol

**Typhoid Vaccine (Immunizing):** 5 cc. and 20 cc vials Each 1 cc. containing 1,000 million killed bacilli (strain 58, the Panama carrier strain), preserved with 0.5 per cent of phenol.

## U. S. STANDARD PRODUCTS CO.

**Typhoid Vaccine:** 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain), 5 cc and 20 cc. vials containing 1,000 million killed bacilli of the same strain per cubic centimeter. Preserved with 0.5 per cent of phenol

DE FROM THE  
E PARATYPHOID

Combined Vaccine.—

Typhoid Mixed Vac

Prophylactic—Mixed

Enteric Vaccine—'A suspension in isotonic solution of sodium chloride or other suitable diluent of killed typhoid bacilli (*Eberthella typhosa*) of a strain selected for high antigenic efficiency and killed paratyphoid A' bacilli (*Salmonella paratyphi*) and killed paratyphoid B bacilli (*Salmonella schottmulleri*)

The vaccine shall contain in 1 cc., at least 1,000 000 000 typhoid organisms and at least 250 000 000 of each of the paratyphoid organisms. It meets the requirements of the 'National Institute of Health of the United States Public Health Service' U S P

For description and standards see the U S Pharmacope under *Vaccinum Typho Paratyphosum*

*Actions and Uses*—Typhoid Paratyphoid Vaccine is of considerable value in the prevention of typhoid fever and paratyphoid fevers due to *Eberthella typhosa*, *Salmonella paratyphi* (*Bacterium paratyphosum A*) and *Salmonella schottmulleri* (*Bacterium paratyphosum B*)

*Dosage*—'Average dose—Hypodermic, for active immunization 0.5 cc. and 1 cc., the latter dose to be repeated' U S P

## ABBOTT LABORATORIES

Ampuls Typhoid-Paratyphoid Bacterin (Prophylactic) 1 cc. in packages of three, one containing 500 million typhoid bacilli (Panama carrier strain 58) and 375 million of paratyphoid bacilli A and B and two each containing 750 million killed typhoid bacilli and 750 million each paratyphoid bacilli A and B

Typhoid-Paratyphoid Bacterin (Prophylactic) vials in packages of ten, 6 cc. and 20 cc. vials, containing 750 million killed typhoid bacilli (Panama carrier strain) and 750 million each of killed paratyphoid bacilli A and B per cubic centimeter

## CUTTER LABORATORIES

Typhoid-Paratyphoid Prophylactic 1 cc. vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of paratyphoid bacilli A and B and two each containing 500 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B, 25 cc. syringe containing 1 000 million killed typhoid bacilli of the same strain and of 500 million each of killed paratyphoid bacilli A and B per cubic centimeter. Preserved with tricresol



THE GILLILAND LABORATORIES, INC.

**Typhoid-Paratyphoid Bacterial Vaccine Immunizing:** 1 cc. vials in packages of three, one containing 500 million killed typhoid bacilli (Rawling's strain or Panama carrier strain 58, as desired) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1,000 million killed typhoid bacilli of either of the same strains and 500 million each of killed paratyphoid bacilli A and B. sets of ten such units each containing in each 1 cc. either of the same strains typhoid bacilli A and B.

LEDERLE LABORATORIES, INC.

**Typhoid Combined Vaccine (Prophylactic):** 1 cc. vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B. and two each containing 1,000 million killed typhoid bacilli each of killed paratyphoid bacilli A and B. vials containing in each 1 cc. of the same strain and 500 million each of killed paratyphoid bacilli A and B.

ELI LILLY AND COMPANY

**Typhoid Mixed Vaccine, Prophylactic:** 1 cc vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1,000

vials; 5 cc. and 20 cc. vials containing in each 1 cc. 1,000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B Preserved with 1.10,000 merthiolate.

THE NATIONAL DRUG CO.

**Typhoid-Paratyphoid Combined Vaccine:** 1 cc vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B, and two each containing 1,000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B, and in packages of thirty, ten containing 500 million killed typhoid bacilli of the same strain and 250 million each of killed paratyphoid bacilli A and B, and twenty containing twice these amounts. 5 cc., 20 cc. and 30 cc. vials containing in each 1 cc. 1,000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B Preserved with 1.10,000 merthiolate

# BACTERIAL VACCINE MADE FROM THE TYPHOID BACILLUS AND THE PARATYPHOID 'A' AND 'B' BACILLI

Typhoid Combined Vaccine.—  
Vaccine Typhoid Mixed Vac-  
atyphoid Prophylactic—Mixed  
in isotonic solution of sodium  
of killed typhoid bacilli (*Eber-*  
d for high antigenic efficiency  
li (*Salmonella paratyphi*) and  
*almonella schottmulleri*)  
1 cc at least 1 000 000 000  
250 000 000 of each of the  
ets the requirements of the

National Institute of Health of the United States Public Health  
Service U S P

For description and standards see the U S Pharmacopeia  
under *Vaccinum Typho Paratyphosum*

*Actions and Uses*—Typhoid Paratyphoid Vaccine is of con-  
siderable value in the prevention of typhoid fever and para-  
typhoid fevers due to *Eberthella typhosa* *Salmonella paratyphi*  
(*Bacterium paratyphosum A*) and *Salmonella schottmulleri*  
(*Bacterium paratyphosum B*)

*Dosage*—Average dose—Hypodermic for active immuniza-  
tion 0.5 cc and 1 cc the latter dose to be repeated once"  
U S P

## ABBOTT LABORATORIES

Ampuls Typhoid Paratyphoid Bacterin (Prophylactic)  
1 cc in packages of three one containing 500 million killed  
typhoid bacilli (Panama carrier strain 58) and 375 million each  
of paratyphoid bacilli A and B and two each containing 1 000  
million killed typhoid bacilli and 750 million each of killed  
paratyphoid bacilli A and B

Typhoid-Paratyphoid Bacterin (Prophylactic) 3 cc.  
vials in packages of ten, 6 cc. and 20 cc. vials containing 1 000  
million killed typhoid bacilli (Panama carrier strain 58) and  
750 million each of killed paratyphoid bacilli A and B per cubic  
centimeter

## CUTTER LABORATORIES

Typhoid-Paratyphoid  
ages of three one contain  
(Panama carrier strain 58)

typhoid bacilli A and B and two each containing 1 000 million  
killed typhoid bacilli of the same strain and 500 million each  
of killed paratyphoid bacilli A and B 2.5 cc syringe and 20 cc.  
vial containing 1 000 million killed typhoid bacilli of the same  
strain and of 500 million each of killed paratyphoid bacilli A  
and B per cubic centimeter Preserved with 0.25 per cent of  
tricresol

## THE GILLILAND LABORATORIES, INC.

**Typhoid-Paratyphoid Bacterial Vaccine Immunizing:** 1 cc. vials in packages of three, one containing 500 million killed typhoid bacilli (Rawling's strain or Panama carrier strain 58, as desired) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1,000 million killed typhoid bacilli of either of the same strains and 500 million each of killed paratyphoid bacilli A and B, and in hospital sets of ten such units each; 5 cc., 10 cc., 20 cc. and 50 cc. vials containing in each 1 cc. 1,000 million killed typhoid bacilli of either of the same strains and 500 million each of killed paratyphoid bacilli A and B. Preserved with 0.25 per cent of cresol.

## LEDERLE LABORATORIES, INC.

**Typhoid Con**  
in packages of 1  
bacilli (Panama  
paratyphoid bac  
million killed ty  
each of killed paratyphoid bacilli A and B; 5 cc. and 20 cc.  
vials containing in each 1 cc. 1,000 million killed typhoid bacilli  
of the same strain and 500 million each of killed paratyphoid  
bacilli A and B

## ELI LILLY AND COMPANY

each of killed paratyphoid bacilli A and B. Preserved with  
1:10,000 merthiolate.

## THE NATIONAL DRUG CO.

**Typhoid-Paratyphoid Combined Vaccine:** 1 cc. vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B, and two each containing 1,000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B, and in packages of thirty, ten containing 500 million killed typhoid bacilli of the same strain and 250 million each of killed paratyphoid bacilli A and B, and twenty containing twice these amounts; 5 cc., 20 cc. and 30 cc. vials containing in each 1 cc. 1,000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B. Preserved with 1:10,000 merthiolate.

**PARKE, DAVIS & COMPANY**

**Typhoid-Paratyphoid Vaccine (Prophylactic).** 1 cc bulbs in packages of three, one containing 500 million killed typhoid bacilli (Rawling's strain and Panama carrier strain 58 in equal proportions) and 250 million each of killed paratyphoid bacilli A and B, and two each containing 1 000 million killed typhoid bacilli of the same strain mixture and 500 million each of killed paratyphoid bacilli A and B, 25 cc. vials in packages of ten, and 20 cc vials containing 1,000 million killed typhoid bacilli of the same strain mixture and 500 million each of killed paratyphoid bacilli A and B per cubic centimeter Preserved with 0.3 per cent of tricresol

**SHARP & DOHME, INC**

**Typho-Bacterin Mixed (Triple Vaccine).** 1 cc vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B, and two each containing 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B and in packages of thirty, ten each containing 500 million killed typhoid bacilli of the same strain and 250 million each of killed paratyphoid bacilli A and B and twenty each containing twice these amounts, 5 cc and 20 cc vials containing in each 1 cc 1,000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B

**E R SQUIBB & SONS**

**Typhoid Vaccine Combined, Immunizing** 1 cc vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 375 million each of killed paratyphoid bacilli A and B, and two each containing 1 000 million killed ty each of killed p thirty, ten each of the same str bacilli A and B 5 cc and 20 cc vials containing in each 1 cc 1,000 million killed typhoid bacilli of the same strain and 750 million each of killed paratyphoid bacilli A and B Preserved with 0.5 per cent of phenol

**THE UPJOHN COMPANY**

**Typhoid-Paratyphoid Mixed Vaccine** 20 cc vials Each 1 cc contains 1 000 million killed typhoid bacilli (Panama carrier strain 58) and 750 million each of killed paratyphoid bacilli A and B Preserved with 0.5 per cent of phenol

**U S STANDARD PRODUCTS CO**

**Typhoid-Paratyphoid Vaccine Combined** 1 cc vials in packages of three, one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 375 million each of killed

paratyphoid bacilli A and B, and two each containing 1,000 million killed typhoid bacilli of the same strain and 750 million each of killed paratyphoid bacilli A and B; 5 cc. and 20 cc. vials containing in each 1 cc. 1,000 million killed typhoid bacilli of the same strain and 750 million each of killed paratyphoid bacilli A and B. Preserved with 0.5 per cent of phenol.

### *Bacterial Vaccines, Mixed*

These contain more than one species of bacteria.

*Actions and Uses*—The employment of bacterial vaccines should be based either on the discovery of the causative micro-organism by careful bacteriologic examination of the patient under treatment or on well established clinical knowledge which has shown the disease present to be regularly due to the activity of a definite germ. As a rule, one organism plays the predominant role and the destruction of the causative agent will effect a cure. In some cases, however, it has been found that two or more organisms are associated in producing the diseased condition. In such cases, a vaccine containing all the known causative antigens has been thought to be indicated. When this etiologic association has been determined by actual bacteriologic examination, a mixture of two autogenous vaccines or two corresponding stock vaccines may have a logical basis. If the bacteriologic examination is omitted, the mixture rests on a purely hypothetical assumption and the method becomes wholly irrational.

While the subject was still in the earlier experimental stage, various mixtures of vaccine, so-called "mixed" vaccines, were admitted to N. N. R. by the Council. As knowledge concerning the action of inadvisable, and the mix unless their evidence. No conditions before being accepted.

## DIAGNOSTIC AGENTS

### TOXINS FOR IMMUNITY TESTS

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S. P.

For description and standards see the U. S. Pharmacopeia under *Toxinum Diphthericum Diagnosticum*.

*Actions and Uses*.—This test is intended to determine those persons who are unimmune to diphtheria. In nonimmune persons a circumscribed area of redness and infiltration from 1 to 2 cm. in diameter develops at the site following injection of 0.1 cc. of

the Schick test material representing  $\frac{1}{50}$  M L D of diphtheria toxin. The reaction occurs in from twenty four to forty eight hours, and is at its height in from forty eight to seventy two hours. It remains for from six to twelve days is followed by slight scaling, and leaves a brownish pigmented spot. In some persons, a pseudoreaction may occur which may be differentiated by its earlier appearance and disappearance, and the fact that it is less circumscribed and is not followed by pigmentation.

Diphtheria toxin diluted for use with isotonic solution of sodium chloride soon loses potency. Dilution of the material should be made only on the day of test. Diphtheria toxin diluted with peptone solution and certain other agents is apparently quite stable.

**Dosage** — Intracutaneous, for determining susceptibility (Schick Test) 0.1 cc of the dilution representing one fiftieth of the minimum lethal dose U S P

#### CUTTER LABORATORIES

**Diphtheria Toxin for the Schick Test** Vial containing a sufficient volume of diphtheria toxin to provide approximately 50 test doses after dilution, packaged with a vial containing sterile isotonic solution of sodium chloride.

**Diphtheria Toxin for the Schick Test, Diluted** 1 cc. vial containing sufficient diluted toxin for 10 tests. Preserved with 0.5 per cent phenol.

#### THE GILLILAND LABORATORIES, INC

**Diphtheria Schick Test Toxin, Diluted** 1 cc. 25 cc and 5 cc vials containing sufficient diluted toxin for 10, 25 and 50 tests respectively also in the form of heat treated diluted toxin in vials containing sufficient material for 10, 25 and 50 control tests respectively.

#### LEDENLE LABORATORIES INC

**Diphtheria Toxin for Schick Test in Peptone Solution** 0.1 cc syringe and 1 cc and 5 cc vials containing sufficient diluted toxin for 1, 10 and 50 tests respectively also in the form of heat treated peptone diluted toxin in packages of one syringe and of one vial containing sufficient material for 1 and 10 control tests respectively.

**Diphtheria Toxin for the Schick Test** Vials containing sufficient volumes of undiluted diphtheria toxin to provide 10 and 100 tests after dilution, respectively each package with a vial containing the amount of sterile diluent.

#### ELI LILLY AND CO

**Diphtheria Toxin** 10 cc vials containing sufficient material for 10 tests, respectively in 0.1 per cent g

**k Test, Diluted** 1 cc vial containing sufficient diluted toxin for 10 tests, respectively in 0.1 per cent g of sodium chloride.

## THE NATIONAL DRUG CO.

**Diphtheria Toxin for Schick Test, Diluted:** 1 cc., 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively; also supplied in the form of heat treated diluted toxin in 1 cc. and 5 cc. vials containing sufficient material for 10 and 50 control tests.

## PARKE, DAVIS &amp; COMPANY

**Diphtheria Toxin Diluted for Schick Test:** 1 cc., 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively; also supplied in the form of heat treated diluted toxin for control tests.

## SHARP &amp; DOHME, INC.

**Diphtheria Toxin for Schick Test, Diluted:** 1 cc., 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively; also supplied in the form of heat treated diluted toxin in 5 cc. vial containing sufficient material for 50 control tests.

## E. R. SQUIBB &amp; SONS

**Diphtheria Toxin for the Schick Test (In Peptone Solution):** 1 cc. and 10 cc. vials containing sufficient diluted toxin for 10 and 100 tests, respectively; preserved with 0.5 per cent of phenol.

**SCARLET FEVER STREPTOCOCCUS TOXIN FOR DICK TEST.**—For definition see this title under Bacterial Toxins.

**Actions and Uses**—The toxin of the hemolytic streptococcus of scarlet fever is used for determination of susceptibility to scarlet fever and for immunization against scarlet fever. The toxin is first carefully standardized on human beings and diluted so that 0.1 cc. represents a skin test dose.

The test dose is injected intracutaneously on the forearm and the degree of susceptibility is determined at the end of from twenty-two to twenty-four hours. An area of reddening 1 cm. or more in diameter constitutes some degree of a positive reaction while a smaller area of reddening is considered negative. Reactions which have appeared but which have entirely faded at the end of twenty-four hours are regarded as negative. Positive reactions fade rapidly and have usually disappeared at the end of from forty-eight to seventy-two hours.

Scarlet fever streptococcus toxin diluted for use will retain its potency for at least two months at room temperature.

## LEDLER LABORATORIES, INC.

**Scarlet Fever Streptococcus Toxin for the Dick Test:** 20 cc. and 110 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests, respectively.

**THE NATIONAL DRUG CO**

**Scarlet Fever Streptococcus Toxin for the Dick Test**  
2 cc and 11 cc vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests respectively

**PARKE, DAVIS & COMPANY**

**Ampul Scarlet Fever Streptococcus Toxin for Dick Test** 2 cc containing sufficient diluted toxin for withdrawal to perform 5 tests

**Scarlet Fever Streptococcus Toxin for Dick Test**  
11 cc vial containing sufficient diluted toxin for withdrawal to perform 50 tests

**SHARP & DOHME, INC**

**Ampul Scarlet Fever Streptococcus Toxin for the Dick Test** 2 cc containing sufficient diluted toxin for withdrawal to perform 5 tests

**Scarlet Fever Streptococcus Toxin for the Dick Test**  
11 cc vial containing sufficient diluted toxin for withdrawal to perform 50 tests

**E R SQUIBB & SONS**

**Scarlet Fever Streptococcus Toxin for Dick Test**  
2 cc and 11 cc vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests respectively Preserved with 0.3 per cent of phenol

**U S STANDARD PRODUCTS CO**

**Ampul Scarlet Fever Streptococcus Toxin for the Dick Test** 2 cc containing sufficient diluted toxin for withdrawal to perform 5 tests

**Scarlet Fever Streptococcus Toxin for the Dick Test**  
11 cc vial containing sufficient diluted toxin for withdrawal to perform 50 tests

**SCARLET FEVER STREPTOCOCCUS ANTI TOXIN FOR SCHULTZ-CHARLTON TEST**—(For definition and descriptions of scarlet fever streptococcus anti toxin see this title under Antitoxins)

*Actions and Uses*—The antitoxic serum of the hemolytic streptococcus of scarlet fever which is used to produce temporary passive immunity and in the treatment of the disease is also used in the performance of a skin test to differentiate the rash of scarlet fever from eruptions due to other causes. When doubt exists as to the diagnosis of scarlet fever (dose of not more than 0.2 neutralizing units) of the exanthematous area for the test. A positive reaction is known as the Schultz Charlton phenomenon and consists in the



or blanching of the rash at the site of injection of scarlet fever antitoxin is, therefore, the result of local neutralization of the toxin of this disease. The reaction usually remains evident for several days or until the rash in general has begun to fade.

#### THE NATIONAL DRUG CO.

Scarlet Fever Streptococcus Antitoxin, Refined and Concentrated: 1 cc. vial containing sufficient antitoxin for five tests.

#### PARKE, DAVIS & COMPANY

Scarlet Fever Streptococcus Antitoxin: 1 cc. vial containing sufficient antitoxin for five tests

#### SQUIBB & DOWME, INC.

Scarlet Fever Streptococcus Antitoxin Concentrated: 1 cc. vial containing sufficient antitoxin for five tests.

#### E. R. SQUIBB & SONS

Scarlet Fever Streptococcus Antitoxin Concentrated: 1 cc. vial containing sufficient antitoxin for ten tests Preserved with 1:20,000 merthiolate and 0.25 per cent of phenol.

**TRICHINELLA EXTRACT.**—Trichinella extract is diluted saline extraction of clean Trichinella larvae prepared by artificial digestion of muscles of heavily infested experimental animals. The extract is adjusted to neutrality and sterilized by filtration

*Actions and Uses*—Trichinella extract is used for making the intradermal diagnostic skin test in the diagnosis of trichinosis. An immediate or delayed type of positive reaction may result from the intradermal injection of 0.1 cc. of the diluted antigen, depending on the duration of the illness.

#### ELI LILLY & COMPANY

Trichinella Extract: Two 1 cc. vials, one vial of Trichinella Extract, 1:10,000 dilution in isotonic solution of sodium chloride; and one control vial of isotonic solution of sodium chloride used as extracting fluid. Both extract and control solution contain Merthiolate (Sodium Ethyl Mercuri Thio-salicylate, Lilly), 1:20,000, as a preservative.

**TUBERCULINS.**—Many different methods have been used to prepare from the tubercle bacillus (*Mycobacterium tuberculosis*) substances which might be used in the diagnosis or treatment of tuberculosis. These have been, in general, called tuber-

culins, and a few of the more prominent are enumerated here

prepared in exactly the same manner. A tuberculin, designated *Purified Protein Derivative*, has been prepared within the last few years and is now extensively employed as a standard against which all

Tubercu of tuberculous  
infection ates that infec-  
tion with great majority

of people who have been infected by tubercle bacilli react to tuberculin, so that the tuberculin test is a valuable procedure in epidemiological investigations. However, a small proportion of people who have been infected do not react, and this fact must be taken into account in epidemiological studies. Patients with far advanced or rapidly progressive disease may not react, and, on the other hand, persons who have made a complete recovery from slight tuberculous infection may also be negative to tuberculin, also in the presence of febrile disease, as in measles, the capacity to react may be temporarily abolished.

Tuberculin has its widest usage at the present time in tuberculosis case-finding. Its use is based on the assumption that practically all persons with clinical tuberculosis react to tuberculin. The tuberculin test is cheaper than roentgenological examination with standard size film and therefore if it is negative is a measure of economy, obviating the necessity of the more costly examination.

In cases of pulmonary or glandular disease of obscure etiology, particularly in children, the tuberculin test is of value, for in such cases, within the limitations set in the preceding paragraph, failure to react to tuberculin excludes tuberculosis in the diagnosis.

In recent years the use of tuberculin in the treatment of tuberculosis has declined greatly. At present tuberculin is more commonly employed in the treatment of nonpulmonary than pulmonary tuberculosis, although individual practice varies, and a few physicians use this form of therapy routinely in pulmonary cases. Treatment is generally carried out by beginning with a small dose, not large enough to cause any constitutional disturbance, and increasing the dosage gradually in injections at intervals of a few days or weeks. Ordinarily old tuberculin is employed, but the other preparations listed in the following paragraphs are used occasionally. The tuberculin treatment is not a true form of immunization. The basis for treatment lies, first, in the fact that the substance, properly used, causes a mild focal reaction at the site of infection leading gradually

to fibrosis, and, second, in the fact that frequently repeated injection gradually desensitizes the body temporarily. Desensitization to tuberculin is believed to prevent destructive reactions when spread of tubercle bacilli occurs in the body.

*Danger from therapeutic use of tuberculin.* This susceptibility varies enormously in different individuals and at different stages of the treatment, entirely out of relation to the progress of the disease. The use of tuberculin in treatment therefore requires special knowledge and experience. The doses ordinarily used in diagnosis rarely lead to constitutional reaction.

**PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN.**—This type of tuberculin is made from a preparation analogous to old tuberculin, differing chiefly in that a non-protein medium is used instead of glycerol bouillon for the growth of tubercle bacilli. The culture fluid and bacilli after ten weeks of growth are heated as in the preparation of old tuberculin, and the bacilli are filtered off and the filtrate concentrated. After this all constituents of the original medium and all diffusible products of bacillary growth are removed by ultrafiltration, a method of pressure dialysis, and what is believed to be the active principle of tuberculin is precipitated by ammonium sulfate at  $pH$  7.0 or trichloroacetic acid. The precipitate is reprecipitated, washed and dried. It is dispensed in solid, stable form permitting the preparation of solutions of definite concentration.

The method of making, as with old tuberculin, is described under the heading of purified protein derivative of tuberculin are employed. The method of reading reactions is the same as that given in the section on old tuberculin.

SHARP & DOHME, INC.

1.5 cc., 125 cc. and 30 cc., respectively, of restored solution in either the first test strength or the second test strength

culin Koch — Concentrated sterile solution in a special products of growth of the *terculosis*) and should contain about 50 per cent of glycerin. It complies with the requirements of the National Institute of Health of the United States Public Health Service "U S P".

For description and standards see the U S Pharmacopoeia under *Tuberculinum Pristinum*.

**Actions and Uses** — For diagnosis, old tuberculin is used most commonly by intracutaneous injection (Mantoux test) or cutaneously by application to a scarified spot on the skin (von Pirquet test). It may also be used in the form of an ointment or paste applied directly (Moro test) or through the medium of an absorbent material or patch (patch test). The latter method has gained in popularity in recent years. Inflammation at the site of application is evidence that at some time the patient has been infected with tubercle bacilli. In such cases the reaction is called positive.

The intracutaneous (Mantoux) test is most commonly employed. Concentrated old tuberculin is diluted under sterile precautions so that 0.1 cc (the quantity to be injected) will contain 0.01 cmm of old tuberculin (commonly but erroneously called 0.01 mg). Dilution of the tuberculin should be made on the day of test.

The diluted material should be injected intracutaneously into the skin of the flexor surface of the forearm. A 1 cc tuberculin syringe and a sharp 26 gauge one half inch needle are used.

The reactions are read 48 to 72 hours after injection. In ordinary practice, if the reaction is negative following a dose of 0.01 cmm, a second dose of 1.0 cmm is injected into the opposite forearm. Occasionally, for extra precaution, an intermediate dose of 0.1 cmm is employed and sometimes this dose only is used. The latter practice saves time, but occasionally moderately severe reactions may occur, and it is generally recognized that a number of persons who would be positive to 1.0 cmm do not react to 0.1 cmm. In the absence of a reaction following the last dose of tuberculin the patient is regarded as negative. The reaction consists in a papule of edema 5 mm in diameter with a surrounding zone of redness at the point of the tuberculin injection. If there is no edema or induration the reaction should be considered negative. This reaction ordinarily reaches its height in forty eight hours.

For treatment, from one one hundred millionth (0.00000001) to one millionth (0.000001) cc may be used as the initial dose and not more than two doses a week should be given.

The patch test is a modification of the Moro percutaneous test may be used for infants and children wherever there is objection to the use of the needle. Filter paper saturated with tuberculin and dried is affixed in contact with the skin after cleansing with acetone or ether. The patch test must be kept

dry. The test is read after 48 hours. A positive reaction consists of a sharply circumscribed, reddened, and infiltrated area with follicular elevations. The patch test is equivalent to the first strength (0.01 cmm) of old tuberculin intracutaneously. Therefore, if negative, a second test with 0.1 cmm. or 1.0 cmm. of old tuberculin may be performed by intracutaneous injection.

#### CUTTER LABORATORIES

**Tuberculin for the Cutaneous Reaction (Pirquet's):** Capillary tubes in packages of three. Preserved with 0.5 per cent phenol.

**Tuberculin Old (Tuberculin O. T.):** 1 cc. vial of concentrated tuberculin (human type); also supplied in serial dilutions ranging from 0.01 to 100 mg per cubic centimeter. Preserved with 0.5 per cent phenol.

#### THE GILLILAND LABORATORIES, INC.

**Intracutaneous Tuberculin for the Mantoux Test:** 1 cc vial containing diluted tuberculin sufficient for ten tests. Each 0.1 cc. represents 0.1 mg. of tuberculin.

**Original Tuberculin, O. T.:** 1 cc. and 3 cc. vials

**Tuberculin Solution for the Pirquet Cutaneous Diagnostic Test:** Capillary tubes each containing sufficient old tuberculin for one test in packages of 1, 5 and 10 tubes.

**Undiluted Tuberculin, Old:** Syringe containing concentrated old tuberculin supplied with three vials of diluent for the preparation of dilutions 1:100 (1 cc. of which represents 10 mg. of tuberculin), 1:1,000 (1 cc. of which represents 1 mg. of tuberculin) and 1:10,000 (1 cc. of which represents 0.1 mg of tuberculin).

#### LEDERLE LABORATORIES, INC.

**Intracutaneous Tuberculin for the Mantoux Test:** Vial containing old tuberculin supplied with a vial containing isotonic solution of sodium chloride sufficient to make 1 cc containing 1 mg. of tuberculin.

**Tuberculin Pirquet Test (O. T.):** Capillary tubes containing old tuberculin in packages of three accompanied with three scarifiers and in packages of ten.

**Tuberculin Old (Koch's):** 1 cc. container of tuberculin.

**Tuberculin Patch Test (Vollmer):** Cellophane wrapped, assembled adhesive strip having one test and one control square each of filter paper saturated with concentrated old tuberculin and concentrated uninoculated broth, respectively.

U. S. patent 2,190,745 (Feb. 20, 1940; expires 1957).

#### LILI LILLY & COMPANY

**Old Tuberculin, Human Strain Concentrated:** 1 cc. vials containing 1 Gm. of tuberculin or containing a stated

amount of concentrated tuberculin for making dilutions containing from 0.001 mg. to 100 mg. per cubic centimeter, each packaged with a vial of physiological solution of sodium chloride for making serial dilutions

**Pirquet Test** Capillary tubes each containing old tuberculin sufficient for one test, in packages of three.

**Tuberculin Ointment for the Moro Percutaneous Test** 2 Gm. collapsible tube containing equal parts of old tuberculin and wool fat

**Tuberculin Ointment (Wolff)** 2 Gm. collapsible tube containing a dried, triturated, sterile glycerin broth culture (four weeks growth) of human tubercle bacilli (H 37) packaged with a 2 Gm. collapsible tube of control material for use as a tuberculin test by the patch method. Preserved with 0.4 per cent of phenol

#### THE NATIONAL DRUG CO

**Ampuls Tuberculin Intracutaneous for Mantoux Test** 1 cc. of a 1:1000 dilution of old tuberculin sufficient for ten initial tests and of a 1:100 dilution sufficient for the same number of secondary tests in packages of one ampul containing the first dilution, of one ampul containing the second dilution with an accompanying vial of glycerin bouillon for the same number of control tests and of two ampuls each containing the first and second dilutions, respectively, 5 cc. ampuls containing either the first dilution sufficient for 50 initial tests or containing the second dilution for the same number of secondary tests packaged with a vial of glycerin bouillon for an equal number of control tests

**Tuberculin Old (Human)** 1 cc. vial containing 1 Gm. of tuberculin Koch, 10 cc. ampul vials in packages of five serial dilutions containing in each 2 minims 0.001 mg., 0.01 mg., 0.1 mg., 1 mg. and 20 mg. respectively, of old tuberculin.

**Pirquet Test for Tuberculosis** Capillary tubes in packages of one, three and ten, each accompanied with capillary tubes containing glycerin bouillon for control

#### PARKE, DAVIS & COMPANY

**Tuberculin Old (Koch)** 1 cc. bulbs, preserved with 50 per cent of glycerin.

**Tuberculin Old and Control for the Pirquet Test** Sealed tubes in packages of three, each tube containing tuberculin sufficient for one test, accompanied by three tubes of bouillon for control, preserved with 50 per cent of glycerin

**Tuberculin for the Mantoux Test** 10 cc. vial containing 0.01 cc. of old tuberculin (Koch) packaged with a 10 cc. vial of diluent. A filtrate from bouillon cultures from both human and bovine preserved with 50 per cent of glycerin

## SHARP &amp; DOHME, INC.

**Tuberculin Old (O. T.):** 1 cc. vial; 8 cc. vials in packages of five serial dilutions, the first containing in each 2 minims, 0.001 mg., the others each containing a concentration ten times that of the preceding dilution.

**Pirquet Test for Tuberculosis:** Capillary tubes containing sufficient old tuberculin for one test in packages of 1 and 10, accompanied with an equal number of tubes of concentrated glycerin bouillon for use as a control.

**NEW TUBERCULIN, B. E.—Tuberculinum Novum B. E.—Bazillenemulsion, Koch.—Bacilli Emulsion**—Bacilli emulsion is practically a bacterial vaccine. It is made by suspending one part of pulverized tubercle bacilli, *Mycobacterium tuberculosis*, in 100 parts of distilled water and 100 parts of glycerin. One cc. thus corresponds to 5 mg. of tubercle bacilli. It is a white, fairly permanent emulsion, but should be shaken thoroughly before making dilutions. New tuberculin, B. E., is occasionally used in the treatment of tuberculosis.

## PARKE, DAVIS &amp; COMPANY

**Tuberculin B. E. (Concentrated):** Bulbs of bacillus emulsion containing 1 mg. of dry tubercle solids per cubic centimeter; preserved with 50 per cent of glycerin.

## SHARP &amp; DOHME, INC.

**Bacillen Emulsion B. E.:** 1 cc. vial.

## NEW

Novum 1  
bacterial

dried, granular, . . . . .  
The diluent is adjusted so that one tablet dissolved therein will represent the desired amount of new tuberculin B. E. dried, per cc.

## PARKE, DAVIS &amp; COMPANY

**Tablets Tuberculin B. E. (Dried):** 0.0001 mg., 0.001 mg., 0.01 mg., 0.1 mg. and 1 mg., preserved with 50 per cent of glycerin. Supplied in vials of ten tablets each.

disintegration. The water insoluble material is suspended in glycerin and water. The final product contains the residue of 10 mg. of dried tubercle bacilli in each cc. of fluid.

New tuberculin is an uncolored, slightly opalescent liquid. It is used occasionally in the treatment of tuberculosis.

**NEW TUBERCULIN T R DRIED**—*Tuberculinum Novum T R Siccum*—*Tuberculin Residue (Dried)*—The mass culture of *Mycobacterium tuberculosis* is repeatedly ground and washed until all water soluble material has been removed. The residue is then ground to complete disintegration, dried, mixed with a suitable base and made into tablets. Each tablet represents a definite amount of dry tubercle bacilli.

**TUBERCULIN DENYS**—*Tuberculinum Denys*—*Tuberculine Bouillon Filtré*—*Bouillon Filtrate Tuberculin*—This is prepared like old tuberculin without the prolonged heating and concentration that is; it is simply a glycerin broth culture of the tubercle bacillus *Mycobacterium tuberculosis* passed through a porcelain filter. It contains all the soluble products of the growth of the tubercle bacillus.

**PARKE DAVIS & COMPANY**

**Tuberculin B F (Human)** 1 cc rubber stoppered bulbs.  
A tuberculin Denys prepared with human cultures preserved with 0.4 per cent of cresol.



## CHAPTER XXI

# VITAMINS AND VITAMIN PREPARATIONS FOR PROPHYLACTIC AND THERA- PEUTIC USE

### VITAMINS

The investigations of nutrition that have been initiated since the second decade of the present century have afforded an entirely new outlook upon many disorders, some of which have long been suspected to be of dietary origin. This is due to the scientific demonstration that factors other than proteins, carbohydrates, fats and minerals are essential for the preservation of bodily well-being and physiologic function. These factors are designated at the present time as vitamins.

The absence of any one of the vitamins from a diet which is satisfactory in other respects leads to the development of a typical syndrome which is called a "deficiency disease." These diseases may be as striking in their manifestations as are the direct result of underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine, iron, calcium or phosphorus. A striking illustration of a "deficiency disease" is presented by scurvy. This can be entirely averted or effectively cured by the inclusion of foods which contain vitamin C (ascorbic acid) in the diet. It has been clearly established by convincing experiments that the prophylactic or remedial agent—the antiscorbutic substance—is a definite chemical entity having the composition  $C_6H_8O_6$ . The vitamin is present in many articles used as food, such as fresh vegetables and fruits, yet entirely lacking in others such as the common cereals and grains. Ascorbic acid is readily destroyed by heat under certain conditions, notably in an alkaline medium and in the presence of oxygen. However, foods can be processed without serious loss of ascorbic acid if precautions are taken to exclude air and if the reaction of the food is not unfavorable for the preservation of the vitamin.

The foregoing illustration will suffice to indicate the characteristics of a vitamin—a substance essential for maintenance of normal metabolic functions, not identical with the more familiar nutrients, not synthesized in the human body, and therefore to

vitamin activity have been isolated and identified. There are now available many commercial preparations in pure synthetic form having the same physiologic properties as the naturally-occurring compounds.

For convenience the designations, vitamins A, B, C and D etc., have arisen. Scurvy, beriberi, rickets, pellagra, and xeroph-

thalnia have been  
 certainty to the lac  
 curative substances  
 the antiscorbutic vita  
 antirachitic vitamin  
 the antixerophthalmia

physiology of the vitamins can now be found in the newest textbooks on physiological chemistry and nutrition. The problems raised thereby are the subject of active discussion and extensive investigation so that with respect to many features only tentative conclusions should be announced at this time.

Chemical, physical and microbiologic methods are now in general use for the determination of vitamins in pharmaceutical products, but, biologic assays must be used for vitamin D and for checking other determinations. To facilitate such assays and to make uniform the expression of vitamin content, the Health Organization of the League of Nations has sponsored the preparation and distribution of standards for vitamins A, B<sub>1</sub>, C and D. The International unit for each of these vitamins is defined in terms of the biological activity of a specific quantity of the respective standard. The U S P units for vitamins A, B<sub>1</sub>, C and D are identical in value with the International units. The United States Pharmacopoeial Convention also distributes prototype standards for these four vitamins and in addition reference standards for riboflavin and nicotinic acid.

The Council has decided that when practicable, vitamin content should be stated in milligrams in preference to micrograms or units. This action was prompted by recognition that confusing practices have grown up in the industry concerning representations for the vitamin content of products. The vitamin content of some products has heretofore been expressed in micrograms even though the term is wholly unfamiliar to the laity. As a result of this the purchaser may be led to believe that a product has a higher vitamin content when so represented than if units or milligrams were used. For instance one milligram of vitamin B<sub>1</sub> equals 333 U S P or International units or 1000 micrograms. A very similar situation prevails with respect to riboflavin. The decision is applicable to ascorbic acid, thiamine, riboflavin, nicotinic acid, and vitamin K preparations, and will be applied to other vitamins for which no units have been established. Vitamins A and vitamin D content should be expressed in U S P units.

While the requirements of the infant for vitamins A, B<sub>1</sub>, C and D have been fairly well established, we do not have as much evidence that bears directly on the adult requirements for vitamins A and D. Ordinarily there is no reason why a properly selected diet should not afford an adequate supply of the requisite vitamins. Furthermore, with the exception of pellagra, there is no evidence of any noteworthy prevalence in this country of conditions in adults that might properly be ascribed to a severe deficiency of one or more vitamins. How

ever, it must be admitted that under circumstances bringing about a highly restricted dietary regimen and leading to "one-sided" diets a relative shortage of some of the vitamins does at times arise. In almost all such instances the situation can be properly corrected by prescription of appropriate foods. Occasionally, and particularly with infants, a corrective result may be more effectively secured by the administration of products especially rich in the desired vitamin; for example, cod liver oil as a dietary adjunct in the prevention or treatment of rickets, and orange juice in the relief of scurvy.

concentrations of the desired potent principle that they may represent or to exceptionally desirable dosage forms. Multivitamin preparations, particularly capsules, have come into very extensive use in recent years. In most of these preparations the proportion of vitamins present has borne no relationship to established therapeutic dosages, nor to normal requirements for the vitamins. For various reasons the Council has opposed the use of such preparations. The Council will consider for acceptance multivitamin preparations in which the vitamin content is in proportion to the daily needs for the vitamins. This subject is discussed in a report published in the Journal (119:948, July 18, 1942).

## GENERAL PROVISIONS AND LABELING REQUIREMENTS

*Statement of Vitamin Potency*—When vitamin A or vitamin D potency is expressed, it must be in U. S. P. units. When the vitamin content of preparations of ascorbic acid, thiamine, riboflavin, nicotinic acid, nicotinamide, pyridoxine, menadione and similar vitamin K preparations is expressed, it must be in milligrams and not in micrograms, gammas, or units.

Vitamin preparations which supply in the recommended daily intake not more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act, must be labeled to show the proportion of the minimum daily requirements supplied in the recommended daily intake.

Vitamin preparations which supply in each unit (tablet, capsule, etc.) or in the recommended daily intake more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act will be accepted if they are advertised only to the physician. To meet the requirements of the Food, Drug and Cosmetic Act with respect to adequate directions for use, such preparations must bear the statement ". . . daily, or as prescribed by the physician. This dosage is in excess of the quantity needed

for prevention of deficiency," or a more detailed statement of directions for use

The above labeling requirements are exemplified in the following outline of statements which should appear on the main panel of the label

#### STATEMENTS REQUIRED ON MAIN LABEL

##### *For Preparations Supplying More Than Three Times the Minimum Daily Requirements*

Quantity of contents	50 tablets
Common or usual name	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily	10 milligrams
Adequate directions for use	Dose One tablet daily or as prescribed by the physician This dosage is in excess of the quantity needed for prevention of thiamine deficiency
Name and place of business	John Doe 550 Broad Street Chicago Illinois

##### *For Preparations Supplying Three Times the Minimum Daily Requirements or Less*

Quantity of contents	100 tablets
Common or usual name	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily	1 milligram
Dose	This is optional
Proportion of minimum daily requirement	1 tablet will supply the minimum daily requirement for an adult
Name and place of business	John Doe 550 Broad Street Chicago Illinois

#### General Allowable Claims for Vitamins

*Growth*—A deficiency of any food essential will undoubtedly lead to retardation of growth. This is true of each of the essential vitamins but it is equally true of each of the essential amino acids, minerals and of energy yielding compounds. Statements conveying the impression that one vitamin is more important than another vitamin or food essential in promoting growth are therefore considered misleading and objectionable.

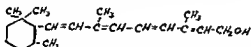
have not been shown to be more closely correlated to specific deficiencies than to the organisms to which the body may be exposed. Secondary infections are characteristic of conditions resulting from severe vitamin deficiency. Investigations have failed to show that the administration of vitamins far in excess of bodily needs makes one more resistant to diseases than the ingestion of quantities which are just sufficient to meet normal metabolic requirements.

### Vitamin A

The term "vitamin A" has been applied to any one of several substances or to a mixture of them producing a certain demonstrable specific physiological effect. It seems to have been definitely established that the precursors of vitamin A, are produced in the plant kingdom, and ingestion of these substances by most animals results in varying degree (depending on the species of animal and the precursor

tion of vitamin A has not been established, but the pathologic picture which results from varying degrees of deficiency has been the subject of extensive investigation.

Vitamin A has the following structural formula:



The claims recognized for vitamin A shall be recognized for the precursors of vitamin A only under conditions specified elsewhere for Carotene

*Allowable Claims.*—1. Evidence for the existence of vitamin A and its role in human nutrition is based on the fact that a characteristic eye disease, usually called xerophthalmia, results from a deficiency of this vitamin.

2. It is generally agreed that the first symptom or at least one of the first clinical symptoms of vitamin A deficiency is night-blindness, or nyctalopia. For this type of night blindness vitamin A is a specific. Cases of nyctalopia exist which do not respond to treatment with vitamin A. These may be due to

congenital defects or to other diseases than avitaminosis 'A'. In view of present knowledge, the claim is not acceptable that the administration of vitamin A to drivers of automobiles will diminish the chance of accident from driving at night.

3 Vitamin A is reported to be effective in the treatment of certain types of hyperkeratosis of the skin of persons suffering from severe deficiency of vitamin A.

4 Vitamin A in excess of normal requirements has not been shown to be of value in the prevention of colds, influenza and such infections.

5 There is at the present time inadequate evidence to warrant the claim that the ingestion of sufficient vitamin A will prevent the formation of renal calculi in man or that it is useful in the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, or ulcerative conditions of the skin.

### The Vitamin B Complex

The term Vitamin B Complex is applied to a group of substances which have been shown to be constituents of what was formerly called vitamin B. Intensive investigations have produced an ever changing picture of the constituents which comprise the complex. At this writing six compounds recognized as members of the vitamin B complex have been identified and are being manufactured by synthetic processes. They are:

Thiamine (vitamin B<sub>1</sub>) or Thiamine Hydrochloride (vitamin B<sub>1</sub> hydrochloride), the antiberiberi vitamin which prevents beriberi in man and polyneuritis in animals. See following section on Thiamine for further discussion.

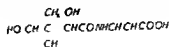
Riboflavin, ..  
 living cells ..  
 ing a deficien ..  
 section on Riboflavin for further discussion.

Nicotinic Acid (amide), (P P factor), a nutritional factor effective in the treatment of human pellagra. See following section on Nicotinic Acid and Nicotinic Acid Amide for further discussion.

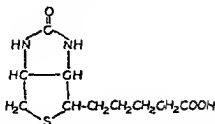
Pyridoxine (Vitamin B<sub>6</sub>) or Pyridoxine Hydrochloride (vitamin B<sub>6</sub> hydrochloride) a factor for the prevention of a nutritional dermatosis in rats. There is yet no satisfactory evidence relating to its therapeutic value for man.

Pantothenic Acid a factor for the prevention of a nutritional dermatosis in chicks and necessary for the growth of rats. Its value in human nutrition has not been demonstrated.

Pantothenic acid has the following structural formula



Biotin has the following structural formula.



This compound combines with a protein-like substance in raw egg white called "avidin." In suitable diets containing large proportions of raw egg white the rat or chick develops characteristic skin lesions and growth is retarded. These symptoms can be prevented by ingestion of biotin. The practical significance of these observations is not established because there is evidence that sufficient quantities of biotin for metabolic requirements may be synthesized in the intestinal tract.

"Vitamin Bc," "norite eluate factor" and "folic acid" are names a not iden preventi pounds.

dyscrasias produced in the rat by the feeding of large amounts of some of the sulfonamide drugs.

In addition to these five substances there are other factors which have been described as producing various symptoms and conditions in a number of species. None of these has been shown to have any importance in human nutrition.

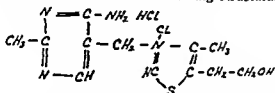
### Thiamine

The name "Thiamin" for vitamin B<sub>1</sub> was proposed by Dr. R. R. Williams who elucidated the structure of the compound. This name and "Thiamine Chloride" for the chloride hydrochloride

the term "Thiamine" as being synonymous with vitamin B<sub>1</sub>.

This vitamin is recognized as being of fundamental importance in connection with the disease beriberi. The pure compound was first isolated in 1927. Since that time its chemical constitution has been established and it is now being manufactured synthetically. It is usually prepared as the hydrochloride and then has the formula C<sub>12</sub>H<sub>17</sub>ON<sub>4</sub>S Cl HCl.

Thiamine hydrochloride has the following structural formula



The International Conference on Vitamin Standardization has adopted crystalline vitamin B<sub>1</sub> hydrochloride as the standard for this vitamin and defined the unit as the biological activity of three micrograms of this standard

*Allo table Claims*—1 Thiamine is of value in correcting and preventing beriberi

The consensus of opinion of the students of beriberi is that this disease with its nervous and cardiovascular manifestation is due primarily to an insufficient supply of thiamine. It is probable that in the majority of instances of human beriberi there are also deficiencies of food constituents other than thiamine. There are conditions which probably could be designated as latent beriberi, it does not seem wise at this time to attempt the formulation of a definite statement covering such conditions other than that presented in Item 5

2 Thiamine may be cited as of value in correcting and preventing anorexia of dietary origin in certain cases

There are many causes of anorexia, some referable to infections and the reactions thereto others to organic disorders and still others related to faulty diet. Where there is no rather obvious cause of anorexia in question other than a possible dietary one it is permissible to claim that thiamine may be of therapeutic value when the condition to be treated is due to a deficiency of that vitamin

3 The administration of the ordinary diet may be a conditions indicating inter alia the vitamins

The present status of research on the clinical use of thiamine for specific diseases other than beriberi and for infant feeding is such that *definite* claims for therapeutic value in relation to such diseases cannot be recognized. Its use may be indicated however in such restricted conditions as pernicious vomiting of pregnancy, tube feedings through a jejunal fistula and the like because the above permitted statement applies to such conditions and gives an intelligent basis for such therapy

4 While it has not been established that thiamine deficiency is the sole cause of conditions described as alcoholic neuritis the neuritis of pregnancy and the neuritis of pellagra there is some definite evidence of the value of this vitamin in the treatment of these conditions. Vague representations with respect to the value of thiamine in the treatment of other types of neuritis are not permissible



5. Thiamine deficiency in animals is associated with dysfunctions .

effective : . . . . .

vascular . . . . .

deficiency. . . . .

other type . . . . .

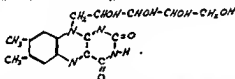
beriberi heart coexist. Administration of thiamine is justified in these patients.

6 It appears that there is an increased requirement for thiamine when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism, or vigorous muscular activity.

### Riboflavin

Riboflavin, the empirical formula of which is  $C_{17}H_{20}N_4O_6$ , was formerly known as Vitamin G, Vitamin B<sub>2</sub>, or Lactoflavin. The chemical nature of the vitamin was established in 1935.

Riboflavin has the following structural formula:



*Allowable Claims.*—1. Riboflavin is recognized as a specific in the treatment of certain characteristic lesions of the tongue, the lips, and the face. The symptoms may be described briefly as follows: A typical glossitis may often be observed before other signs of riboflavin deficiency are present. In contrast to the glossitis of pellagra, the tongue is clean, the papillae are flattened or mushroom-shaped rather than atrophic, and the color is definitely purplish-red or magenta instead of being scarlet as in nicotinic acid deficiency. As the disease progresses, the lips become reddened, then shiny and denuded, with maceration and fissuring at the angles of the mouth (cheilosis). Frequently, seborrheic follicular keratoses occur at the nasolabial folds and even over the nose and forehead. The above symptoms are promptly alleviated by the administration of adequate amounts of riboflavin.

2 Riboflavin deficiency is responsible for certain ocular manifestations characterized by itching, burning and a sensation of roughness of the eyes (keratitis), accompanied by mild photophobia. The anatomical changes may vary from a superficial invasion of the cornea by capillaries to an extensive vascular proliferation, with or without infiltration, opacity, and exudate formation. These symptoms, when due to a riboflavin deficiency, are relieved promptly by the administration of the vitamin.

3 It is permissible to recommend the use of riboflavin for the alleviation of symptoms of riboflavin deficiency encountered in other diseases, notably pellagra.

### Nicotinic Acid and Nicotinamide

Nicotinic acid ( $C_6H_5ON$ ) and nicotinamide ( $C_6H_5ON_2$ ) are of fundamental importance in the treatment of pellagra. The terms niacin and niacin amide are now officially recognized as synonyms for these chemical names. The pure compounds have been known for many years, but not until recently were they recognized as therapeutic agents. In 1938 the Council voted to accept nicotinic acid and nicotinamide for purposes of standardization and clinical experimentation. Sufficient evidence has now been accumulated to demonstrate the usefulness of these drugs. Administration of relatively large doses of nicotinic acid produces a marked flushing of the face and neck. There is an unpleasant sensation but the reaction is transient and apparently harmless. This effect is not observed following the administration of nicotinamide. For parenteral use nicotinamide is the drug of choice.

Nicotinic acid has the following structural formula



Nicotinamide has the following structural formula



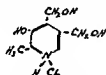
*Allowable Claims*—1 Nicotinic acid and nicotinamide are recognized as specifics only in the treatment of pellagra. Their administration in appropriate doses lead to the disappearance of all alimentary, dermal and other lesions, characteristic of the disease, to a return to normal of the porphyrin and porphyrin like pigments of the urine and to a profound improvement in the mental symptoms when the latter are the result of an inadequate intake of nicotinic acid and nicotinamide. These compounds are without influence upon the polyneuritis or cheilosis so frequently observed in pellagrous patients. In such cases it

may be necessary to insure the presence in the diet of foods rich in vitamin B<sub>1</sub> or B<sub>6</sub>, or to administer thiamine hydrochloride, riboflavin or both.

### Pyridoxine

The terms "pyridoxine" and "pyridoxine hydrochloride" are synonymous with "vitamin B<sub>6</sub>" and "vitamin B<sub>6</sub> hydrochloride." Pyridoxine has been available for too brief an interval of time and in insufficient quantities to permit its clinical evaluation. Further study of the clinical value of this compound is necessary before definite claims will be permitted. Pyridoxine is accepted to assure the availability of a preparation of satisfactory composition for investigational use.

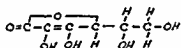
Pyridoxine hydrochloride has the following structural formula:



### Ascorbic Acid (Cevitic Acid)

Suboptimal intakes of ascorbic acid result in the development of clinical and pathologic phenomena to which the descriptive term scurvy has been applied.

Ascorbic acid has the following structural formula:



All pure ascorbic acid that has been used in pharmaceutical products in recent years has been prepared synthetically. The international unit for ascorbic acid, which was formerly defined as the vitamin C activity of 0.1 cc. of lemon juice, is now defined as the activity of 0.05 mg. of ascorbic acid. This is the quantity of ascorbic acid usually found in 0.1 cc. of lemon juice or orange juice. \*

In planning diets for infants who do not receive breast milk, and for small children, it is generally advisable to make special provision for a source of ascorbic acid such as orange juice because (a) the concentration of ascorbic acid in fresh cow's milk is only about one-fourth of the concentration in mother's milk, and (b) the vitamin in most foods is very sensitive to destruction by oxidation.

*Allowable Claims*—1. Ascorbic acid is acceptable for the correction and prevention of scurvy. Definite claims for the

therapeutic value of ascorbic acid should be permitted only in relation to scurvy until further clinical or experimental evidence has substantiated its usefulness in other states

2 It may be permissible under certain conditions to refer to the therapeutic value of ascorbic acid in early and latent scurvy. Convincing clinical evidence has established that this state does occur. It would be well to emphasize the fact that the diagnosis rests, however, on the basis of roentgenologic evidences in the long bones, the blood level, and possibly failure to excrete an optimum amount of ascorbic acid in the urine.

3 Dental caries, pyorrhea, certain gum infections, anorexia, anemia, undernutrition and infection alone are not in themselves sufficient indications of ascorbic acid deficiency but according to experimental and clinical investigation may be concomitant signs of ascorbic acid deficiency. Therefore it is permissible to accept the claim for the therapeutic value of ascorbic acid in these symptomatic conditions *only when* it is definitely stated that they are the consequences of a deficiency or suboptimal amount of ascorbic acid or when there is a pathologic interference with assimilation of the amount necessary for the preservation of health.

4 Because ascorbic acid is a dietary essential its administration in concentrated form is of value in conditions where difficulty is encountered in introducing it orally or in utilizing ordinary foods in the usual way. Ascorbic acid is accepted as an essential dietary constituent in infant feeding but it should not be accepted for use in the treatment of diseases except

5 Dosage forms of ascorbic acid offered for clinical use must state the potency in terms of milligrams.

6 A reasonable general statement regarding allowable claims for ascorbic acid would be as follows:

An optimum amount of ascorbic acid should be supplied at all ages for its therapeutic value in preventing the development of acute or latent scurvy.

Claims for the therapeutic value of ascorbic acid may be accepted when the agent is described as a corrective measure for scurvy due to a demonstrable absence or a suboptimal quantity in the diet or in cases in which it is definitely known that there is interference with the absorption of an optimal amount.

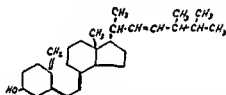
Advertising of ascorbic acid for such symptoms as failure to gain in weight or stoppage of growth, anorexia, anemia, infections, symptoms referable to the central nervous system or hemorrhagic conditions cannot be accepted unless it is definitely stated that the symptoms are referable to a demonstrable deficiency of ascorbic acid.

Ascorbic acid is easily decomposed in the presence of certain other substances; therefore, care should be exercised against administering it (or orange juice) in mixtures, or by any procedure which renders it ineffective.

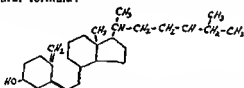
### Vitamin D

The term "vitamin D" which have a function in phosphorus. Two forms been isolated. One of the in pure crystalline form as one of the products of the ultra-violet irradiation of ergosterol. The two forms of vitamin D, as well as some of the other products of irradiated ergosterol, possess anti-rachitic potency. They also tend to elevate the level of serum calcium, an effect which varies, however, with the different substances and which does not parallel the anti-rachitic effect.

Vitamin D<sub>2</sub> has the following structural formula:



Activated 7-dehydro-cholesterol (vitamin D<sub>3</sub>) has the following structural formula:



Some reports have appeared claiming clinical improvement in chronic arthritis and in certain allergic disorders as a result of the use of massive doses of vitamin D. Critical examination of these reports reveals little to warrant the belief that the clinical effects claimed are specific. There is suggestive clinical evidence that the use of massive doses of vitamin D may cause improvement in some cases of psoriasis, but the effect is not yet well enough established to justify a claim for such use. The Council believes that further studies should be conducted, but, because of the possible toxic effects of large doses of vitamin D, it is necessary that such studies should be made only in clinics where close supervision is possible. The Council also

holds there is not sufficient evidence to warrant the acceptance of viosterol preparations of high potency for use in the treatment of arthritis.

Another suggested use of massive doses of vitamin D is in the treatment of refractory rickets, that is, occasional cases of rickets which do not respond to treatment with the usual dosages or even much larger dosages of vitamin D. In some of these cases the rickets is due to a disturbance of the acid base balance and has been successfully treated by administration of sodium bicarbonate or a sodium citrate citric acid mixture. Massive doses of vitamin D have proved effective in the control in others. The quantity of vitamin D needed may be so large that it borders on the dosages of vitamin D that are definitely toxic, and such treatment should not be undertaken without first exploring other possibilities or without careful observation for signs of toxicity. Some investigators believe it desirable to examine the urine daily for calcium casts, albumin and red blood cells while the maintenance dose is being established. Others believe less frequent examination is necessary. After the dose is established weekly examination, using the Sulkowitch test for excessive excretion of calcium, is sufficient. The blood should be examined weekly or oftener to avoid a rise of calcium above 12 mg per hundred cubic centimeters if the dosage exceeds 20,000 units daily for the infant or 50,000 units for a child. If anorexia or nausea should appear, the child must be brought promptly to the attention of the physician and vitamin D administration should be discontinued. When the maintenance dose has been established, operative procedures to correct rachitic deformities may precipitate a temporary state of toxicity and the blood levels of calcium must be watched closely.

It is now well established that certain substances derived from activation products of ergosterol and cholesterol are effective in raising the level of serum calcium. This result is achieved in part by mobilization of calcium from the bones but also by an increased absorption of calcium, only Vitamin D<sub>2</sub> (calciferol) and dihydrotachysterol have received extensive clinical trials. Either of these substances may be administered

is superior to the other in the management of hypoparathyroidism. During their use frequent determinations of serum calcium are desirable, the Sulkowitch test, by which the excretion of calcium into the urine is observed is helpful and is so simple that it may be performed by the patient. Its routine use during treatment will reduce the number of necessary determinations of serum calcium.

Treatment of parathyroid insufficiency is commonly initiated with relatively large doses of the activated sterols, followed by

smaller maintenance doses. The management of acute parathyroid tetany may require from 2 to 8 mg. of pure dihydrotachysterol which is approximately equivalent to 10 to 40 mg. or 400,000 to 1,600,000 international units of vitamin D. The amount of the substances necessary for daily maintenance varies greatly in individual cases but averages between 0.6 and 1.0 mg. of pure dihydrotachysterol or 30 to 50 mg. (133,333 to 200,000 international units) of vitamin D.

*Allowable Claims*—1. Vitamin D is recognized as a specific in the treatment of infantile rickets, spasmodophilia (infantile tetany) and osteomalacia, diseases which are manifestations of abnormal calcium and phosphorus metabolism. Vitamin D is valuable in the prevention as well as in the curative treatment of these diseases. Complications such as renal insufficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections, especially of the gastrointestinal tract, vitamin D may prove ineffective because poorly absorbed.

2. Direct exposure of the skin to ultraviolet light from the sun or from artificial sources results in the formation of vitamin D within the organism but the Council cannot recognize statements or implications that vitamin D has all beneficial effects of exposure to sunshine.

3. There is clinical evidence to justify the statement that vitamin D plays an important role in tooth formation. Its other values in relationship to teeth are still subject to investigation.

4. Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical utilization of calcium and phosphorus and also that the undesirable effects of improper ratios of calcium and phosphorus in the diet can largely be overcome by normal intake of vitamin D. The importance of these observations in their application to man is not entirely apparent because of the lack of adequate clinical evidence showing the availability of different forms of calcium and phosphorus, but it may be stated that vitamin D has a favorable influence on calcium and phosphorus metabolism.

5. Because of its effect upon the level of serum calcium, vitamin D has been used in correcting the hypocalcemia of parathyroid tetany. Satisfactory effects may be obtained with sufficient doses either of vitamin D<sub>2</sub> (calciferol) or of dihydrotachysterol, a derivative of one of the products resulting from the irradiation of ergosterol. When vitamin D preparations are employed for the correction of hypocalcemia, patients must be under constant observation since the elevation of serum calcium above normal levels may be accompanied by serious or even fatal effects.

6. Clinical evidence does not warrant the claim that massive doses of vitamin D are of benefit in chronic arthritis, in allergic disorders, or in psoriasis. If representations are made for use

of massive doses of vitamin D in the treatment of refractory rickets they must be accompanied by adequate precautions with respect to the danger of toxic effects and how they can be avoided as indicated in the paragraph immediately preceding the allowable claims for vitamin D

### Vitamin E

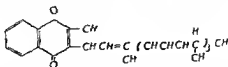
For nearly two decades it has been known that vitamin E must be included in the diet of the rat to insure successful reproduction. There are at least three naturally occurring compounds which have vitamin E activity—alpha, beta and gamma tocopherol. There have been comparatively few clinical studies dealing with the role of vitamin E in human physiology and they have not led to very definite conclusions. There seems to be agreement that the vitamin is of no value in the treatment of sterility. There are indications that it may be of value in the treatment of habitual abortion but further studies are necessary to clarify the picture.

Recently there has been renewed interest with respect to vitamin E owing to reports that administration of alpha tocopherol and other preparations of vitamin E have produced beneficial results in the treatment of some cases of degenerative diseases such as amyotrophic lateral sclerosis. This is not substantiated in any way by recent clinical evidence.

### Vitamin K

Vitamin K was discovered and named by Dam of Copenhagen in 1935 when he observed in newly hatched chicks a fatal hemorrhagic diathesis which could be cured or prevented by the administration of a nonsaponifiable nonsterol fraction of hog liver or alfalfa. Later it was observed that the delayed clotting time of the blood was due to low prothrombin content. Investigations have shown that there are at least two naturally occurring substances having a naphthoquinone nucleus which have similar physiologic properties and they are referred to as vitamin K<sub>1</sub> and vitamin K<sub>2</sub>. Their empirical formulas are as follows: K<sub>1</sub> C<sub>31</sub>H<sub>46</sub>O<sub>2</sub>, K<sub>2</sub> C<sub>34</sub>H<sub>54</sub>O<sub>2</sub>.

Vitamin K<sub>1</sub> has the following structural formula



Recently a number of naphthoquinone derivatives have been synthesized which produce a wide range of vitamin K activity some being even more potent than pure vitamin K<sub>1</sub> or vitamin K<sub>2</sub> and some of them water soluble. They have been referred to as vitamin K analogues.



The Council has recognized the term "Menadione" for the compound 2-methyl-1,4 naphthoquinone. "Menadione" has the following structural formula:



There is now adequate demonstration that prothrombin deficiency in the blood of man may result from interference with the absorption of vitamin K. Some of the fat-soluble vitamins, including vitamin K, are not absorbed when the flow of bile is obstructed, and synthesis of prothrombin by the liver does not occur unless vitamin K is available. Obviously it is necessary to administer bile salts with vitamin K when prothrombin deficiency is due to bile obstruction and the vitamin is given orally. While bile salts are necessary for the absorption of most of the oil preparations of vitamin K and its analogues, there are now available certain water-soluble materials which obviate the necessity for concurrent administration of bile salts. It has also been demonstrated that the incidence of hemorrhage in the newborn can be reduced by administering to the mother before delivery, preparations having vitamin K activity. The full significance of this observation is not as yet apparent.

*Allowable Claims.*—Vitamin K, both in its crude form and in certain related naphthoquinones with analogous antihemorrhagic activity, seems to have a specific effect on prothrombin deficiency occurring under certain sets of circumstances:

- 1 In primary dietary deficiency of vitamin K which, while admittedly rare, does exist.
2. In obstructive jaundice, in which vitamin K has proved to have an extraordinary protective effect against hemorrhage diathesis.

also affected in a specific manner by vitamin K.

5. In the treatment of the physiological hypoprothrombinemia of the newborn, which exists during the first week of life, the vitamin and its analogues seem to be a specific. It seems now fairly well established that the vitamin itself or the naphtho-

quinones, when administered parenterally to a woman during labor, in amounts as small as  $\frac{1}{2}$  to 2 mg, insures that the newborn infant will have a normal amount of prothrombin in the circulating blood. These doses can also be given parenterally to the newborn infant and will produce the same effect.

## VITAMIN PREPARATIONS

### Vitamin A Preparations

For allowable claims see preceding article, Vitamin A. Vitamin A is found in fish liver oils (which see). The provitamin A carotene gives the effects of vitamin A when ingested.

**CAROTENE—Pro Vitamin A**—A hydrocarbon having the empiric formula  $C_{40}H_{56}$  which occurs in three isomeric forms referred to respectively as alpha beta and gamma carotene. The alpha form is optically active and the others are not. The beta form appears to predominate in nature, and the gamma is found in the smallest quantities but usually a mixture of the different forms occurs. The crystals are readily oxidized. They should be kept in a vacuum or in an inert gas in the dark at a low temperature. The International unit for vitamin A adopted at the Second International Conference on Vitamin Standardization 1934 is defined as the vitamin A activity of 0.6 microgram of beta carotene. There is considerable scientific evidence indicating that alpha and gamma carotene have one-half the vitamin A activity of beta carotene. The Council has reached the following decision with respect to the use of the term Pro vitamin A as a synonym for carotene: (1) that the term A Pro vitamin A be regarded as a synonym for alpha beta or gamma carotene or for cryptoxanthin and that the synonym Pro vitamin A be adopted and used in New and Nonofficial Remedies for any combination of two or more of these and (2) that when this synonym is used on the label of any accepted product it appear in brackets after the Council name with a statement of the vitamin A potency of the product.

**Actions and Uses**—It appears that at least a portion of the carotene ingested is converted in the liver into vitamin A. Carotene therefore has actions similar to those of vitamin A. As carotene may be a mixture of the alpha, beta and gamma forms its relative efficiency may vary according to the ratio of these components. Evidence is not available on which to base the exact conversion factor of carotene in terms of clinical vitamin A effect. Much depends on the conditions for absorption of pigments. The absorption of carotene and to a lesser degree that of vitamin A is decreased in steatorrhea and diarrhea both acute and chronic. Liquid petrolatum being a good solvent for carotene prevents its absorption and should not be administered together with preparations of carotene. In view of the fact that cases of carotenemia have arisen from overdosage the Council warns against the administration of too

large doses of carotene. The vitamin potencies stated are on the basis of biological assays and not on physical and chemical measurements establishing the identity and purity of the product.

*Dosage.*—See statement under vitamin A and D Preparations. Carotene is generally administered in the form of carotene dissolved in an oily solution.

#### S. M. A. CORPORATION

**Carotene in Oil:** 50 cc. bottle. A solution containing carotene in cottonseed oil. It is biologically assayed to have in each gram a vitamin A potency of not less than 7,500 units, U. S. P. Accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

**Carotene with Vitamin D Concentrate in Oil:** 50 cc bottle. A solution in cottonseed oil of carotene with sufficient vitamin D concentrate to bring the assayed potency to not less than 1,000 U. S. P. units per gram. When assayed for vitamin A potency by the method of the U. S. P. it is required to contain in each gram not less than 7,500 units.

**Carotene and Vitamin D Concentrate in Cod Liver Oil:** 4 oz. bottle. A solution of carotene in cod liver oil, adjusted by the addition of sufficient vitamin D concentrate so that it will assay at not less than 250 units of vitamin D (U. S. P.) per gram. The mixture is assayed to have a vitamin A potency of not less than 2,000 units U. S. P. per gram. The carotene is the source of not less than 650 of these units.

The vitamin D concentrate is used by license of Columbia University under U. S. patent 1,678,454 (July 24, 1928; expires 1945).

**OLEOVITAMIN A.—Natural Vitamin A in Oil.**—"Fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of vitamin A concentrate in fish liver oil or in an edible vegetable oil. The vitamin A shall be obtained from natural (animal) sources. Oleovitamin A contains in each Gm. not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A, and not more than 1,000 U. S. P. units of vitamin D." U. S. P.

For description and standards see the U. S. Pharmacopeia under Oleovitamin A and Capsulae Oleovitaminiae A.

*Actions, Uses and Dosage.* See vitamin A and D preparations.  
**ABBOTT LABORATORIES**

**Vitamin A Capsules:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from natural fish liver oils.

#### INTERNATIONAL VITAMIN CORPORATION

**Oleo Vitamin A Capsules:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

#### WALKER VITAMIN PRODUCTS, INC.

**Oleo Vitamin A Capsules:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

**WHITE LABORATORIES, INC**

**White's Oleo-Blend Vitamin A Capsules** Each capsule contains 25,000 U S P units of vitamin A derived from fish liver oils

**Vitamin B Complex Preparations**

For allowable claims see preceding article Vitamin B Complex

The Council will consider for acceptance the following types of preparations containing mixtures of the components of the vitamin B complex

(1) Mixtures of pure thiamine, riboflavin and nicotinic acid providing in the recommended daily intake 1 milligram thiamine, 1.5 to 2 milligrams riboflavin 10 milligrams nicotinic acid, or simple multiples thereof

(2) Dry brewer's yeast having the following minimum vitamin content per gram 0.12 milligram thiamine, 0.04 milligram riboflavin, and 0.250 milligram nicotinic acid

(3) Dried brewer's yeast as described under (2), to which has been added riboflavin and nicotinic acid in such quantities that for each milligram of thiamine contained in the finished product there are present 1.5 to 2 milligrams of riboflavin and 10 milligrams of nicotinic acid.

(4) A concentrate of the vitamin B complex from brewer's yeast as described under (2), and providing in the recommended daily intake 1 milligram of thiamine (or a simple multiple thereof) and corresponding proportions of other known vitamins of yeast

(5) A concentrate of the vitamin B complex from liver containing in each gram not less than 0.25 milligram of riboflavin

(6) A concentrate of the vitamin B complex from brewer's yeast fortified with riboflavin and nicotinic acid and providing in the recommended daily intake 1 milligram thiamine, 1.5 to 2 milligrams riboflavin and 10 milligrams nicotinic acid or simple multiples thereof

(7) A concentrate of the vitamin B complex from rice polishings fortified with riboflavin and nicotinic acid providing in the recommended daily intake 1 milligram thiamine, 1.5 to 2 milligrams of riboflavin and 10 milligrams of nicotinic acid or simple multiples thereof

**YEAST EXTRACT CONTAINING VITAMIN B COMPLEX**—A mixture of water soluble extractives of dried brewers' yeast

*Actions and Uses*—Yeast extract containing vitamin B complex is proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex in the diet.

*Dosage*—Infants 2 cc to 4 cc of the liquid preparation daily, children 4 cc to 12 cc of the liquid preparation or 2 to 6 tablets daily, adults 12 cc to 24 cc of the liquid preparation or 6 to 12 tablets daily

## ABBOTT LABORATORIES

**Brewers' Yeast Powder Fortified with Riboflavin and Nicotinic Acid:** Contains dried brewers' yeast (*Saccharomyces cerevisiae*), debitterized, fortified with crystalline riboflavin and nicotinic acid to contain in each gram vitamin B<sub>2</sub> 50 U. S. P. units (0.15 mg.), riboflavin 0.3 mg. and nicotinic acid 1.5 mg. Daily prophylactic dose for infants,  $\frac{1}{2}$  level teaspoon; children 1 to 6 years old, 1 level teaspoon; children 6 to 12 years old,  $1\frac{1}{2}$  level teaspoons; older children and adults, 2 level teaspoons mixed with water, milk or fruit juices.

**Brewers' Yeast Tablets, 0.4 Gm., Fortified with Riboflavin and Nicotinic Acid:** Each tablet contains Abbott's Brewers' Yeast Powder Fortified with Riboflavin and Nicotinic Acid 0.4 Gm., providing in each tablet vitamin B<sub>2</sub> 20 U. S. P. units (0.06 mg.), riboflavin 0.12 mg., nicotinic acid 0.6 mg. Average daily dose, as a supplement to the diet, for children 6 to 12 years old, 6 tablets; older children and adults, 9 tablets; therapeutic doses must be determined for each patient.

**Brewer's Yeast Tablets, 0.5 Gm. Fortified with Riboflavin and Nicotinic Acid:** Each tablet contains 0.5 Gm. of dried brewer's yeast (*Saccharomyces cerevisiae*), debitterized, fortified with crystalline riboflavin and nicotinic acid to contain in each tablet vitamin B<sub>2</sub> 35 U. S. P. units (0.1 mg.), riboflavin 0.2 mg. and nicotinic acid 1 mg. Prophylactic dose for adults 10 tablets daily; therapeutic doses must be determined for each patient.

*Preparation—*

Abbott's brewers' yeast tablets are prepared from a selected strain of *Saccharomyces cerevisiae* especially cultured. The yeast cells are washed and dried, the dry powder containing approximately 5 per cent of moisture, and compressed into tablets.

The vitamin B<sub>2</sub> content of the tablets is determined by comparison with the international standard by the modified Smith rat curative method. The vitamin G content is determined by the Sherman-Bourquin method.

## SCIENTIFIC SUGARS Co.

**Kinney's Yeast Extract Containing Vitamin B Com-**

plex

**Kinney's Yeast Extract (Vitamin B Complex) Tablets:** 0.325 Gm. (5 grains). Each tablet contains dehydrated yeast extract, 0.325 Gm., equivalent to not less than 0.15 mg. (50 I. U.) of thiamine hydrochloride and not less than 0.06 mg. (25 Sherman-Bourquin units) of riboflavin.

*Preparation—*

Kinney's yeast extract containing vitamin B complex is prepared by extracting specially cultured dried brewers' yeast in an aqueous medium under proper conditions of pH control. The extract is con-

centrated and clarified. It may then be preserved in liquid form by the addition of an equal volume of a mixture of equal parts of glycerin and simple syrup or dehydrated to powder form.

The vitamin B<sub>1</sub> content is determined by comparison with the International Standard according to the Cowgill Pigeon Weight Maintenance Technique as outlined in *The Vitamin B Requirement of Man* by Cowgill chapter IV. At regular intervals samples are also compared with the International Standard according to the rat growth method of Sherman and Spohn as outlined in *The Vitamins* by Sherman and Smith edition 2, page 99. The vitamin G content is determined by the Sherman-Bourquin Method as outlined in *The Vitamins* by Sherman and Smith edition 2 page 133. The glycerin content in liquid preparations is estimated according to the method described in *Methods of Analysis* A O A C 1930 page 302 chapter XXVIII paragraph 55.

### Thiamine Preparations

For allowable claims see preceding article, Thiamine

**THIAMINE HYDROCHLORIDE-U. S. P.**—Thiamine chloride—Vitamin B<sub>1</sub> hydrochloride—Vitamin B<sub>1</sub>—C<sub>12</sub>H<sub>17</sub>ClN.  
OS HCl U. S. P.—Betabion

For description and standards see the U. S. Pharmacopoeia under *Thiaminae Hydrochloridum* and *Tabellae Thiaminae Hydrochloridi*. One mg. of thiamine hydrochloride is equivalent to 333 U. S. P. units.

Acceptance of tablets thiamine hydrochloride will be limited to ½, 1, 3, 5 and 10 mg. of thiamine hydrochloride per tablet and the acceptance of solutions thiamine hydrochloride for parenteral use will be limited to 1, 5, 10 and 50 mg. thiamine hydrochloride per cc.

*Actions and Uses*—See preceding article, Thiamine

*Dosage*—The minimum daily requirement of thiamine for an adult appears to be approximately 1 mg., and the optimum intake is said to lie between 15 and 25 mg. For the child, the optimum intake may be calculated from the caloric requirement by allowing at least 0.03 milligram for each 100 calories. In the well balanced diet the thiamine requirement should be obtained from the food.

When pharmaceutical preparations of thiamine hydrochloride are prescribed the minimum daily prophylactic dosage for the infant should not be less than 0.15 mg. and for the adult should not be less than 1 mg. There appears to be no satisfactory evidence that prophylactic dosages in excess of 0.5 mg. for the infant and 3 mg. for the adult are indicated. Evidence on which to base dosages in the treatment of acute deficiencies is meager. There are indications that doses of the order of 10 to 50 mg. may be advantageous in specific instances. There is no evidence that doses considerably in excess of these quantities have a toxic effect.

#### ABBOTT LABORATORIES

Tablets Thiamine Hydrochloride 0.3 mg. 1 mg. 3 mg.  
5 mg. 6 mg. 9 mg. 10 mg. and 12 mg.

Ampoule Solution Thiamine Hydrochloride, 6 mg. per cc.: 1 cc.

Ampoule Solution Thiamine Hydrochloride, 10 mg. per cc.: 1 cc.

Sterile Isotonic Solution Thiamine Hydrochloride, 10 mg. per cc.: 10 cc. bottle. Each cc. contains thiamine hydrochloride 0.01 Gm., sodium chloride 0.0057 Gm., and chlorobutanol 0.005 Gm., in chemically pure water. This preparation is for parenteral administration.

Sterile Solution Thiamine Hydrochloride, 30 mg. per cc.: 5 cc. bottle. Preserved with 0.5 per cent chlorobutanol.

Sterile Solution Thiamine Hydrochloride, 50 mg. per cc.: 5 cc. bottle. Each cc. contains thiamine hydrochloride 0.05 Gm., and chlorobutanol 0.005 Gm., in chemically pure water. This preparation is for parenteral administration.

#### GEORGE A. BREON & COMPANY, INC.

Tablets Thiamine Hydrochloride: 1 mg. and 5 mg.

Solution Thiamine Hydrochloride, 10 mg. per cc.: 10 cc. vial. Contains sodium chloride 7.5 mg. per cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Thiamine Hydrochloride, 30 mg. per cc.: 5 cc. vial. Contains sodium chloride 5.3 mg. per cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Thiamine Hydrochloride, 50 mg. per cc.: 5 cc. and 30 cc. vials. Contains sodium chloride 3.65 mg. per cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Thiamine Hydrochloride, 100 mg. per cc.: 30 cc. vial. Preserved with 0.5 per cent chlorobutanol.

#### BURROUGHS WELLCOME & Co., INC.

Hypoloid Solution Thiamine Hydrochloride, 10 mg. per cc.: 25 cc. vials. Preserved with phenol 0.5 per cent.

Hypoloid Solution Thiamine Hydrochloride, 50 mg. per cc.: 5 cc. and 25 cc. vials. Preserved with phenol 0.5 per cent.

Tabloid Thiamine Hydrochloride: 1 mg., 5 mg. and 10 mg.

#### THE DRUG PRODUCTS Co., INC.

Pulvoids Thiamine Hydrochloride: 1 mg., 3 mg.

Ampul Hyposol Solution of Thiamine Hydrochloride, 6.66 mg. per cc.: 1 cc.

Ampul Hyposol Solution of Thiamine Hydrochloride, 10 mg. per cc.: 1 cc.

Ampul Hyposol Solution of Thiamine Hydrochloride, 33.33 mg. per cc.: 1 cc.

**Ampul Hyposol Solution of Thiamine Hydrochloride** 50 mg per cc 1 cc

**Hyposol Solution of Thiamine Hydrochloride**, 6.66 mg per cc 10 cc and 30 cc vials Preserved with 0.5 per cent of chlorobutanol

**Hyposol Solution of Thiamine Hydrochloride**, 10 mg per cc 10 cc and 30 cc vials Preserved with 0.5 per cent of chlorobutanol

**Hyposol Solution of Thiamine Hydrochloride**, 33.33 mg per cc 10 cc and 30 cc vials Preserved with 0.5 mg of chlorobutanol

**Hyposol Solution of Thiamine Hydrochloride**, 50 mg per cc 10 cc and 30 cc vials Preserved with 5 mg of chlorobutanol

#### ENDO PRODUCTS, INC

**Tablets Thiamine Hydrochloride** 1 mg 3 mg and 5 mg

**Ampul Solution Thiamine Hydrochloride**, 1 mg per cc 1 cc Preserved with 1 per cent benzyl alcohol

**Ampul Solution Thiamine Hydrochloride**, 6 mg per cc 1 cc Preserved with 1 per cent benzyl alcohol

**Ampul Solution Thiamine Hydrochloride**, 10 mg per cc 1 cc Preserved with 1 per cent benzyl alcohol

**Ampul Solution Thiamine Hydrochloride**, 15 mg per cc 1 cc Preserved with 1 per cent benzyl alcohol

**Ampul Solution Thiamine Hydrochloride**, 30 mg per cc 1 cc Preserved with 1 per cent benzyl alcohol

**Solution Thiamine Hydrochloride**, 10 mg per cc 10 cc 25 cc and 50 cc vials Preserved with 1 per cent benzyl alcohol

**Solution Thiamine Hydrochloride**, 30 mg per cc 10 cc 25 cc and 50 cc vials Preserved with 1 per cent benzyl alcohol

**Solution Thiamine Hydrochloride**, 50 mg per cc 5 cc 10 cc and 25 cc vials Preserved with 1 per cent benzyl alcohol

#### FLINT EATON & COMPANY

**Tablets Thiamine Hydrochloride** 1 mg 5 mg and 10 mg

**Ampul Solution Thiamine Hydrochloride**, 10 mg per cc 1 cc

**Solution Thiamine Hydrochloride**, 10 mg per cc 15 cc vial

**Solution Thiamine Hydrochloride**, 25 mg per cc 15 cc vial

**Solution Thiamine Hydrochloride** 50 mg per cc 15 cc vial



## INTERNATIONAL VITAMIN CORPORATION

**Tablets Thiamine Hydrochloride:** 0.5 mg., 1 mg., 3.3 mg., 5 mg. and 10 mg.

## THE LAKESIDE LABORATORIES, INC.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg.

**Ampul Solution Thiamine Hydrochloride,** 10 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

**Solution Thiamine Hydrochloride,** 10 mg. per cc.: 15 cc vial. Preserved with 0.5 per cent of chlorobutanol.

**Ampul Solution Thiamine Hydrochloride,** 25 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

**Solution Thiamine Hydrochloride,** 25 mg. per cc.: 15 cc vial. Preserved with 0.5 per cent of chlorobutanol.

**Ampul Solution Thiamine Hydrochloride,** 50 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

**Solution Thiamine Hydrochloride,** 50 mg. per cc.: 15 cc and 50 cc vials. Preserved with 0.5 per cent of chlorobutanol.

**Solution Thiamine Hydrochloride,** 150 mg. per cc.: 5 cc vial. Preserved with 0.5 per cent of chlorobutanol.

## MEAD JOHNSON AND COMPANY

**Tablets Thiamine Hydrochloride:** 1 mg. and 3 mg.

## MERCK &amp; Co, INC.

**Betabion (Powder):** Thiamine hydrochloride, 0.1 Gm. and 1 Gm. bottles, sealed tubes 0.01 Gm.

**Ampul Betabion (Powder):** 0.01 Gm.

U. S. trademark 336,518

## THE WM. S. MERRELL COMPANY

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

**Ampul Solution Thiamine Hydrochloride,** 5 mg. per cc.: 1 cc.

## THE NATIONAL DRUG CO.

**Tablets Thiamine Hydrochloride:** 0.1 mg., 1 mg., 3.3 mg. and 6 mg.

**Ampuls Solution Thiamine Hydrochloride,** 3.3 mg. per cc.: 1 cc. and 10 cc.

**Ampuls Solution Thiamine Hydrochloride,** 10 mg. per cc.: 1 cc. and 10 cc.

**Solution Thiamine Hydrochloride,** 25 mg. per cc.: 5 cc ampul-vials.

Solution Thiamine Hydrochloride, 50 mg per cc 5 cc ampul vials

Solution Thiamine Hydrochloride, 100 mg per cc 5 cc. ampul vials

#### SCHIEFFELIN & COMPANY

Tablets Thiamine Hydrochloride 0.166 mg 1 mg 3.3 mg and 5 mg

Tablets Thiamine Hydrochloride 10 mg

#### S M A CORPORATION

Tablets Thiamine Hydrochloride 1 mg and 3 mg

Ampul Solution Thiamine Hydrochloride, 3 mg per cc 1 cc

Ampul Solution Thiamine Hydrochloride, 10 mg per cc, 1 cc

#### THE SMITH DORSEY Co

Tablets Thiamine Hydrochloride 1 mg 3.33 mg 5 mg 6.66 mg and 10 mg

Solution Thiamine Hydrochloride 10 cc vials 10 mg per cc, 33.3 mg per cc, 50 mg per cc and 100 mg per cc Each cubic centimeter contains thiamine hydrochloride in an isotonic solution of sodium chloride. Chlorobutanol 0.5 per cent added as a preservative.

#### E R SQUIBB & SONS

Crystals Thiamine Hydrochloride 1 Gm bottle.

Tablets Thiamine Hydrochloride 1 mg 3 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride, 10 mg per cc 5 cc, 10 cc and 25 cc vials Preserved with 0.5 per cent of chlorobutanol

Solution Thiamine Hydrochloride, 25 mg per cc 5 cc vial Preserved with 0.5 per cent of chlorobutanol

Solution Thiamine Hydrochloride, 50 mg per cc 5 cc and 25 cc vials Preserved with 0.5 per cent of chlorobutanol

Solution Thiamine Hydrochloride, 100 mg per cc 5 cc. and 25 cc vials Preserved with 0.5 per cent of chlorobutanol

#### FREDERICK STEARNS & COMPANY

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride 50 mg per cc 5 cc. vial Made isotonic with sodium chloride and preserved with 0.5 per cent of chlorobutanol

## THE UPJOHN COMPANY

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

Ampoule Solution Thiamine Hydrochloride, 5 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

Ampoule Solution Thiamine Hydrochloride, 10 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

Solution Thiamine Hydrochloride, 10 mg. per cc.: 10 cc. and 20 cc. vials. Preserved with 0.5 per cent of chlorobutanol.

Solution Thiamine Hydrochloride, 50 mg. per cc.: 5 cc. and 10 cc. vials. Preserved with 0.5 per cent of chlorobutanol.

## WALKER VITAMIN PRODUCTS, INC.

Solution Thiamine Hydrochloride: 15 cc. and 60 cc. bottles 100 international units vitamin B<sub>1</sub> per drop.

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

## THE WARREN-TEED PRODUCTS COMPANY

Tablets Thiamine Hydrochloride: 10 mg.

## WHITE LABORATORIES, INC.

Tablets Thiamine Hydrochloride: 1 mg., 5 mg. and 10 mg.

## JOHN WYETH &amp; BROTHER, DIVISION WYETH INCORPORATED

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

Ampoule Solution Thiamine Hydrochloride, 1 mg. per cc.: 1 cc. Contains 0.85 per cent of sodium chloride.

Ampoule Solution Thiamine Hydrochloride, 10 mg. per cc.: 1 cc.

Ampoule Solution Thiamine Hydrochloride, 50 mg. per cc.: 5 cc. Preserved with 0.5 per cent of chlorobutanol.

## Riboflavin Preparations

For allowable claims see preceding article, Riboflavin

**RIBOFLAVIN.**—Lactoflavin—Vitamin B<sub>2</sub>—Vitamin G— $C_{17}H_{20}N_4O_6$ . U. S. P.

For description and standards see the U. S. Pharmacopeia under Riboflavinum and Tabellae Riboflavini.

Acceptance of tablets riboflavin will be limited to 1, 2, 5 and 10 mg. of riboflavin per tablet and the acceptance of solutions riboflavin for parenteral use will be limited to 0.2 mg. Riboflavin per cc., except that special consideration will be

given to solutions of higher concentration that may be obtained by the use of other reagents

*Actions and Uses*—See preceding article, Riboflavin

*Dosage*—The optimum intake of riboflavin for an infant appears to be approximately 1 mg per day, and for an adult approximately 3 mg per day. The requirement during pregnancy and lactation is higher. When riboflavin is used therapeutically the dosage varies from 2 to 10 mg per day depending upon the severity of the deficiency. No side effects have been noticed following the administration of relatively large doses.

**ABBOTT LABORATORIES**

Capsules Riboflavin 1 mg and 5 mg

Tablets Riboflavin 1 mg and 5 mg

**GEORGE A. BREON & COMPANY, INC.**

Tablets Riboflavin 1 mg and 5 mg

**BURROUGHS WILLOW & CO., INC.**

Tabloid Riboflavin 1 mg

**HOFFMANN LA ROCHE, INC.**

Ampule Solution Riboflavin, 0.5 mg per cc 2 cc  
Contains urea 10 per cent (w/v) as a stabilizer

**INTERNATIONAL VITAMIN CORPORATION**

Tablets Riboflavin 1 mg and 5 mg

**MEAD JOHNSON AND COMPANY**

Tablets Riboflavin 1 mg

**MERCK & CO., INC.**

Riboflavin (Powder) 1 Gm and 5 Gm bottles

**THE WM. S. MERRELL COMPANY**

Tablets Riboflavin 1 mg

**S. M. A. CORPORATION**

Ampul Solution Riboflavin, 0.2 mg per cc 5 cc  
Tablets Riboflavin 1 mg

**THE SMITH DORSEY COMPANY**

Tablets Riboflavin 3 mg

**THE UPJOHN COMPANY**

Tablets Riboflavin 1 mg

**WALKER VITAMIN PRODUCTS, INC.**

Tablets Riboflavin 1 mg and 5 mg

**THE WARREN FEED PRODUCTS COMPANY**

Tablets Riboflavin 1 mg

## Nicotinic Acid and Nicotinamide Preparations

For allowable claims see preceding article, Nicotinic Acid and Nicotinamide.

**NICOTINIC ACID.**—Niacin—"When dried for three hours over sulfuric acid, contains not less than 99.5 per cent of  $\text{HC}_6\text{H}_4\text{O}_2\text{N}$ ." *U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under *Acidum Nicoticum* and *Tabellae Acidi Nicotini*.



Acceptance of nicotinic acid tablets will be limited to 25, 50 and 100 mg of nicotinic acid per tablet. Solutions of nicotinic acid will not be eligible for acceptance.

*Actions and Uses*—See preceding article, Nicotinic Acid and Nicotinamide.

*Dosage.*—The optimum intake of nicotinic acid has not been established with certainty. However, for adults, it seems to be of the order of 15 to 20 mg. per day. The dose for therapeutic purposes varies considerably from person to person depending upon the severity of the deficiency, and possibly upon other as yet unknown factors. The maximum quantity to be recommended is 500 mg. per day, given in 10 doses of 50 mg. each.

### ABBOTT LABORATORIES

Tablets Nicotinic Acid: 50 mg. and 100 mg.

### AMERICAN PHARMACEUTICAL CO., INC.

Nicotinic Acid (Powder): 1 ounce,  $\frac{1}{4}$  pound and 1 pound packages

Tablets Nicotinic Acid: 25 mg., 50 mg. and 100 mg.

### GEORGE A. BREON & COMPANY, INC.

Tablets Nicotinic Acid: 20 mg. and 100 mg.

### BURROUGHS WELLCOME & CO., INC.

Tabloid Nicotinic Acid: 50 mg. and 100 mg.

### ENDO PRODUCTS, INC.

Ampoule Solution Nicotinic Acid, 1 mg. per cc.: 10 cc.

Ampoule Solution Nicotinic Acid, 2 mg. per cc.: 10 cc.

Ampoule Solution Nicotinic Acid, 10 mg. per cc.: 10 cc.

Tablets Nicotinic Acid: 50 mg. and 100 mg.

### FLINT, EATON & COMPANY

Tablets Nicotinic Acid: 25 mg.

INTERNATIONAL VITAMIN CORPORATION

Tablets Nicotinic Acid 25 mg 50 mg and 100 mg

THE LAKESIDE LABORATORIES, INC

Ampule Solution Nicotinic Acid 1% W/V, 10 mg per cc 10 cc

Tablets Nicotinic Acid 50 mg

MEAO JOHNSON AND COMPANY

Tablets Niacin 20 mg

MERCK & Co., INC

Niacin (*Powder*) Bottles 25 Gm 100 Gm 500 Gm

THE W M S MERRELL COMPANY

Tablets Nicotinic Acid 50 mg

THE NATIONAL DRUG CO

Tablets Nicotinic Acid 20 mg 50 mg and 100 mg

THE NEW YORK QUININE AND CHEMICAL WORKS INC

Nicotinic Acid (*Powder*) bulk

PARKE, DAVIS & COMPANY

Tablets Nicotinic Acid 50 mg and 100 mg

PITMAN MOORE COMPANY

Tablets Nicotinic Acid 20 mg and 50 mg

THE SMITH DORSEY COMPANY

Tablets Nicotinic Acid 50 mg and 100 mg

THE UPJOHN COMPANY

Tablets Nicotinic Acid 20 mg 50 mg and 100 mg

WALKER VITAMIN PRODUCTS INC

Tablets Nicotinic Acid 20 mg 50 mg and 100 mg

THE WARREN TEED PRODUCTS COMPANY

Tablets Niacin 50 mg

JOHN WYETH & BROTHER DIVISION WYETH INCORPORATED

Ampoules Solution Nicotinic Acid, 1 mg per cc 10 cc

Ampoules Solution Nicotinic Acid 2 mg per cc 50 cc

Tablets Nicotinic Acid 25 mg 50 mg and 100 mg

Tablet Triturates Nicotinic Acid 50 mg

**NICOTINAMIDE.**—Nicotinic Acid Amide.—Niacinamide  
—"When dried over sulfuric acid for 18 hours, contains not less  
than 98.5 per cent of  $C_6H_4N_2O$ ." *U. S. P.*

For description and standards see the *U. S. Pharmacopeia*  
under Nicotinamidum and Tabellae Nicotinamidi

of nicotinamide per cubic centimeter

*Actions and Uses*—See preceding article, Nicotinic Acid and  
Nicotinamide

*Dosage*—Same as for nicotinic acid

**ABBOTT LABORATORIES**

Nicotinamide (*Powder*): bulk.

Sterile Ampoules Solution Nicotinamide, 100 mg. per  
2 cc.: 2 cc.

Tablets Nicotinamide: 50 mg. and 100 mg

**GEORGE A. BREON & COMPANY, INC.**

Ampul Solution Nicotinic Acid Amide, 25 mg. per  
cc.: 2 cc.

Tablets Nicotinic Acid Amide: 50 mg

**BURROUGHS WELLCOME & CO., INC.**

Hypoloid Nicotinamide Injection, 100 mg. per cc.: 5 cc  
vial. Preserved with 0.5 per cent chlorobutanol.

**THE DRUG PRODUCTS CO., INC.**

Ampul Hyposol Solution of Nicotinamide, 50 mg. per  
cc.: 1 cc.

Hyposol Solution of Nicotinamide, 50 mg. per cc.:  
10 cc. vial. Preserved with 0.5 per cent of chlorobutanol

Pulvoids Nicotinamide: 50 mg.

**FLINT, EATON & COMPANY**

Tablets Nicotinamide: 50 mg

Sterile Solution Nicotinamide, 50 mg. per cc.: 15 cc  
rubber capped vial.

**INTERNATIONAL VITAMIN CORPORATION**

Tablets Nicotinic Acid Amide: 25 mg. and 50 mg

**THE LAKE-SIDE LABORATORIES, INC.**

Tablets Nicotinamide: 50 mg.

Ampule Solution Nicotinamide, 10% W/V: 1 cc. Each  
cubic centimeter contains 100 mg. of nicotinamide in distilled  
water with 0.5 per cent chlorobutanol

**Solution Nicotinamide 10% W/V** 15 cc vial Each cubic centimeter contains 100 mg of nicotinamide in distilled water with 0.5 per cent chlorobutanol

MERCK & Co, INC

Niacinamide (Powder) 25 Gm 100 Gm 500 Gm

THE WM S MERRELL COMPANY

Nicotinic Acid Amide (Powder) bulk

Tablets Nicotinic Acid Amide 50 mg

THE UPJOHN COMPANY

Nicotinic Acid Amide (Powder) bulk

Tablets Nicotinic Acid Amide 50 mg

Sterile Solution Nicotinic Acid Amide 100 mg 2 cc

WALKER VITAMIN PRODUCTS, INC

Tablets Nicotinamide 20 mg, 50 mg and 100 mg

THE WARRINTEED PRODUCTS COMPANY

Sterile Solution Nicotinamide 50 mg per cc 15 cc vials Chlorobutanol 0.5 per cent added as a preservative.

Tablets Nicotinamide 50 mg

JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED

Tablets Nicotinic Acid Amide 50 mg

### Vitamin B<sub>6</sub>

**PYRIDOXINE HYDROCHLORIDE**—2 methyl 3 hydroxy 4,5 di (hydroxymethyl) pyridine hydrochloride (vitamin B<sub>6</sub> hydrochloride)— $C_8H_{10}O_4N \cdot HCl$  (205.64)

It may be isolated from natural sources or prepared synthetically from ethoxy acetylacetone and cyanoacetamide.

**Actions and Uses**—The nutritive and therapeutic value of pyridoxine hydrochloride has not been definitely established. It has been accepted by the Council for purposes of standardization and experimentation only.

**Dosage**—A dose of 5 to 10 mg daily is suggested.

#### Tests and Standards—

Pyridoxine hydrochloride occurs as a white odorless crystalline powder which melts with decomposition between 200 and 212 C. Under the polarizing microscope it appears as thick birefringent rods and broken fragments. When recrystallized from methanol containing a few drops of concentrated hydrochloric acid needle shaped crystals are obtained which are birefringent and exhibit oblique extinction. In the crystalline state it is reasonably stable to light and air. Aqueous solutions of pyridoxine hydrochloride are stable and may be heated for thirty minutes at 120 C without decomposition. It is soluble in water (22 Gm per hundred cubic centimeters), slightly soluble in 95 per cent ethanol (11 Gm per hundred cubic centimeters), sparingly soluble in acetone, practically insoluble in ether. Aqueous solutions are acidic (pH about 3.0 for a concentration of 10



mg per cubic centimeter), produce a red color with ferric chloride solution, yield a precipitate with phosphotungstic acid solution and yield a precipitate with silver nitrate solution which is insoluble in nitric acid but soluble in ammonia water.

Dissolve a few crystals of pyridoxine hydrochloride in 2 cc. of alcohol. Add 2 drops of 10 per cent ammonium hydroxide solution and 1 cc. of 2,6-dichloroquinone chloroimide solution (0.01 per cent in alcohol). A deep blue color forms on standing.

lead (0.005 per cent as lead)

When dried over sulfuric acid, anhydrous calcium sulfate or anhydrous magnesium perchlorate for twenty-four hours, the loss in weight does not exceed 0.2 per cent.

Determine the carbon and hydrogen content by combustion: the carbon content is not less than 46.5 nor more than 46.9 per cent; the hydrogen content is not less than 5.6 nor more than 6.0 per cent. The residue from the carbon-hydrogen determination, or from an ash determination, does not exceed 0.05 per cent.

Determine the nitrogen content: the amount found is not less than 6.6 nor more than 6.9 per cent.

#### *Method of Assay for Tablets and Solutions*

The following reagents are necessary.

2. Chloroimide Reagent—Dissolve 25.0 mg. 2,6-dichloroquinone chloroimide in 100 cc. of acid-free butanol. If the reagent is to be kept for some time, it must be stored in a brown, glass stoppered bottle at refrigerator temperatures, treated thus, it is stable for about two weeks.

3. Standard Solution—10.0 mg. of dried crystalline pyridoxine hydrochloride is dissolved in exactly 100 cc. of absolute alcohol. If the solution is to be used immediately, 95 per cent ethanol may be employed. (In the absence of a microbalance, a larger quantity may be weighed and appropriate dilutions made from the more concentrated stock solution.)

Procedure—Dilute the pyridoxine hydrochloride solutions to be tested to a final concentration in 0.10 mg. of pyridoxine hydrochloride per cubic centimeter. In the case of tablets, a sufficient number—ten or more—are transferred to a volumetric flask, water added and the flask shaken to disintegrate the tablets. After diluting to the mark, the solution is filtered, the first 25 cc. discarded and the next 25 cc. saved for the test.

In the following procedures the preparation of the standard and unknown must be carried on concurrently to allow the same amount of time for the development of color in the two solutions.

Transfer 5.0 cc. of the solution to be tested (after diluting as indicated) to a 50 cc. volumetric flask. Add 5.0 cc. of the barbital buffer and 20 cc. of ethanol.

Prepare a standard comparison solution by transferring 5.0 cc. of the standard pyridoxine hydrochloride solution to a 50 cc. volumetric flask, adding 5.0 cc. of barbital buffer, 15 cc. of ethanol and 5 cc. of water.

Now add to both solutions 5.0 cc. of butanol-chloroimide reagent, start timing, and shake intermittently for twenty minutes. Dilute to the mark with ethanol and compare in a colorimeter. The pyridoxine hydrochloride found is not less than 93 or more than 107 per cent.

**THE LAKESIDE LABORATORIES, INC.**

Ampuls Pyridoxine Hydrochloride, 50 mg. per cc.: 1 cc.

Pyridoxine Hydrochloride, 50 mg. per cc.: 5 cc. vial

Tablets Pyridoxine Hydrochloride: 5 mg

**MERCK & Co., INC.**Hexabione Hydrochloride (*Crystals*). 50 mg. and 100 mg. sealed tubes

U S trademark 152,230

**THE SMITH-DORSEY Co**

Tablets Pyridoxine Hydrochloride: 1 mg

**THE UPJOHN COMPANY**

Ampoules Sterile Solution Pyridoxine Hydrochloride 50 mg. in 2 cc

Tablets Pyridoxine Hydrochloride: 10 mg

**JOHN WYETH & BROTHER, DIVISION WYETH INCORPORATED**

Ampoules Solution Pyridoxine Hydrochloride: 50 mg. in 1 cc

Tablets Pyridoxine Hydrochloride: 25 mg

**Ascorbic Acid Preparations**

For allowable claims see preceding article, Ascorbic Acid

**ASCORBIC ACID**—Vitamin C—U. S. P.—Cebione—Cevitamic acid.—“Contains, when dried in a vacuum desiccator over sulfuric acid for 3 hours, not less than 99 per cent of  $C_6H_8O_6$ .” U S P

For description and standards see the U S Pharmacopeia under Acidum Ascorbicum and Tabellae Acidi Ascorbici

Ascorbic acid is quite stable, but in impure preparations and in many natural products the vitamin oxidizes on exposure to air or light, and such products should be preserved in an oxygen free atmosphere protected from light.

Acceptance of tablets of ascorbic acid will be limited to 10, 25, 50 and 100 mg. of ascorbic acid per tablet

**Actions and Uses**—See preceding article, Ascorbic Acid**Dosage**—The optimum daily intake of ascorbic acid for an infant appears to be approximately 30 mg., and for an adult approximately 75 mg. Under certain conditions, notably pregnancy and lactation, the requirement of the adult may be as high as 100 or 150 mg.

When pharmaceutical preparations are prescribed, the protective dose for infants is 10 mg. daily, and the therapeutic dose is 30 to 50 mg. daily. The protective dose for adults is 25 mg. daily and the therapeutic dose is 100 to 150 mg. daily. Each 1 mg. is equivalent to 20 international units of vitamin C. No evidence exists that ten fold increases exert detrimental effects.

## ABBOTT LABORATORIES

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg

## AMERICAN PHARMACEUTICAL Co., INC.

Ascorbic Acid (*Crystals*): 1 ounce and 5 ounce packages

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## GEORGE A. BREON &amp; COMPANY, INC.

Tablets Ascorbic Acid: 25 mg. and 100 mg

## BURROUGHS WELLCOME &amp; Co., INC.

Tabloid Ascorbic Acid: 25 mg. and 100 mg

## INTERNATIONAL VITAMIN CORPORATION

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg

## MCKESSON &amp; ROBBINS, INC.

Tablets Ascorbic Acid: 30 mg

## MCNEIL LABORATORIES, INC.

Capsules Ascorbic Acid: 50 mg. and 100 mg

## MEAD JOHNSON AND COMPANY

Tablets Ascorbic Acid: 25 mg. and 100 mg

## MERCK &amp; Co., INC.

Cebione (*Crystals*): bulk

Sealed Tubes Cebione (*Crystals*): 0.1 Gm., 0.5 Gm. and 10 Gm.

Tablets Cebione: 10 mg., 25 mg. and 50 mg

U. S. Trademark 315,171

## THE WM. S. MERRELL COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg

## THE NATIONAL DRUG Co.

Tablets Ascorbic Acid: 25 mg

## PARKE, DAVIS &amp; COMPANY

Tablets Ascorbic Acid: 25 mg. and 100 mg

Glaseptic Ampoules Solution of Ascorbic Acid: 2 cc  
Each cubic centimeter contains 50 mg. of ascorbic acid and  
0.1 per cent of sodium bisulfite added as a preservative

## PITMAN-MOORE COMPANY

Tablets Ascorbic Acid: 50 mg

## SCHIEFFELIN &amp; COMPANY

Tablets Ascorbic Acid. 25 mg. and 50 mg

**S M A CORPORATION**

Tablets Ascorbic Acid 25 mg. and 100 mg

**THE SMITH DORSEY COMPANY**

Tablets Ascorbic Acid 25 mg. and 100 mg

**E R SQUIBB & SONS**

Tablets Ascorbic Acid 25 mg. 50 mg. and 100 mg

**FREDERICK STEARNS & COMPANY**

Tablets Ascorbic Acid 25 mg. 50 mg. and 100 mg

**THE UPJOHN COMPANY**

Tablets Ascorbic Acid 15 mg. 25 mg. 50 mg. and 100 mg

**WALKER VITAMIN PRODUCTS, INC.**

Tablets Ascorbic Acid 25 mg. 50 mg. and 100 mg

**JOHN WALTH & BROTHER DIVISION WYETH INCORPORATED**

Tablets Ascorbic Acid 10 mg. 25 mg. 50 mg. and 100 mg

**SODIUM ASCORBATE**—The sodium salt of cevitamic acid  $C_6H_7O_6Na$

*Actions and Uses*—Sodium ascorbate possesses the activity of ascorbic acid and is preferred when parenteral therapy is indicated

*Dosage*—Same as for ascorbic acid

*Tests and Standards*—

A solution of sodium ascorbate may be prepared by neutralizing a solution of ascorbic acid with sodium hydroxide. The pH of sodium ascorbate solution is between 5.5 and 5.9. The ascorbic acid used in the preparation of Council accepted solutions of sodium ascorbate conforms to the tests and standards for ascorbic acid U. S. P.

**GEORGE A. BREON & COMPANY, INC.**

Ampul Solution Sodium Ascorbate 2 cc. Each 2 cc. contains sodium ascorbate equivalent to 100 mg. (2000 international units) ascorbic acid in sterile aqueous solution

Ampul Solution Sodium Ascorbate 500 mg. in 10 cc.

**Vitamin D Preparations or Preparations Giving Vitamin D Effect**

For allowable claims see preceding article Vitamin D

**COD LIVER OIL WITH VIOSTEROL** (See under Vitamins A and D Preparations)

**HALIBUT LIVER OIL WITH VIOSTEROL** (See under Vitamins A and D Preparations)

**SYNTHETIC OLEOVITAMIN D.**—Vioosterol in Oil (Applying only to Activated Ergosterol in Oil)—U. S. P.—Irradiated Ergosterol in Oil—"A solution of activated ergosterol, or activated 7-dehydro-cholesterol, in an edible vegetable oil. Synthetic Oleovitamin D contains in each Gm. not less than 10,000 U. S. P. units of vitamin D.

Synthetic Oleovitamin D must be labeled to indicate whether it contains activated ergosterol (*Vitamin D<sub>2</sub>* or *Vioosterol*) or whether it contains activated 7-dehydro-cholesterol (*Vitamin D<sub>3</sub>*)." U. S. P. Preparations listed under the title, *Vioosterol in Oil*, contain activated ergosterol.

For description and standards see the U. S. Pharmacopeia under *Oleovitamina D Synthetica*.

*Actions and Uses.*—See preceding article, *Vitamin D*.

*Dosage.*—Daily prophylaxis . . . . .  
drops (approximately 0.1 . . . . .  
and rapidly growing infant . . . . .  
curative dose, 15 to 20 dr . . . . .  
in severe cases, doses in excess of 20 drops may be given . . . . .  
marketed preparations are accompanied by a standard dropper . . . . .  
designed to deliver 3 drops to the minim.

*Preparation*—

*Vioosterol in Oil* is prepared by either of the following methods:

(a) Irradiation of a solution of purified ergosterol by ultra-violet rays under a determined distance and intensity for a definite length of time, under reflux in an inert atmosphere. After irradiation the solution is concentrated and the majority of the unchanged ergosterol is removed. The remaining solvent is distilled in an inert atmosphere and the irradiated ergosterol is dissolved in a known weight of vegetable oil. The resulting oil solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U. S. P. method has a vitamin D potency of not less than 10,000 U. S. P. units per Gm.

U. S. patent 1,680,818 (August 14, 1928, expires 1945) and 1,871,136 (August 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

(b) Activation of purified ergosterol by low velocity electrons, after which the activated ergosterol is separated and dissolved in vegetable oil. The resulting solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U. S. P. method has a vitamin D potency of not less than 10,000 U. S. P. units per Gm.

Manufactured by General Mills, Inc., Special Commodities Division, under license agreement with E. I. du Pont de Nemours & Company. U. S. patent 2,117,160 (May 10, 1938, expires 1955).

**ABBOTT LABORATORIES**

*Vioosterol in Oil*: 5 cc., 20 cc. and 50 cc. bottles. *Vioosterol* in sesame oil.

**HOSPITAL LIQUIDS, INC**

**Vioosterol in Oil** 50 cc bottle Vioosterol in bland vegetable oil

**INTERNATIONAL VITAMIN CORPORATION**

**Vioosterol in Oil** 6 cc, 10 cc and 60 cc bottles Vioosterol in neutral vegetable oil

**MCKENSON & ROBBINS, INC**

**Vioosterol in Oil** 10 cc and 60 cc bottles Vioosterol in neutral vegetable oil

**MEAD JOHNSON AND COMPANY**

**Vioosterol in Oil** 5 cc and 50 cc bottles Vioosterol in corn oil

**THE WM S MERRELL COMPANY**

**Vioosterol in Oil** 6 cc and 60 cc bottles Vioosterol in vegetable oil

**PARKE, DAVIS & COMPANY**

**Vioosterol in Oil** 5 cc and 50 cc bottles Vioosterol in corn oil

**L R SQUIBB & SONS**

**Vioosterol in Oil** 5 cc 20 cc and 50 cc bottles Vioosterol in corn oil

**FREDERIC STEARNS & COMPANY**

**Vioosterol in Oil** 6 cc vials Vioosterol in vegetable oil

**WINTHROP CHEMICAL COMPANY, INC**

**Vioosterol in Oil** 5 cc and 50 cc bottles Vioosterol in sesame oil

**VITAMIN D<sub>2</sub>**—Drisdol—9||10 Ergostatetraene (18 10 5 6 7 8 22 23) of 3 -C<sub>28</sub>H<sub>44</sub>O

Vitamin D<sub>2</sub> may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound it is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D<sub>3</sub>. A method of preparation of vitamin D<sub>2</sub> is given in Addendum 1936 to the British Pharmacopoeia, 1932 page 20. The crystals have a potency of 40 units of vitamin D (U S P) per microgram (For methods of assay see U S P XII p 640)

**Actions and Uses**—For allowable claims see under allowable claims for vitamin D

**Tests and Standards**—

Vitamin D<sub>2</sub> occurs as a colorless odorless acicular crystalline substance. It is insoluble in water soluble in alcohol ether chloroform acetone ethylene glycol and propylene glycol sparingly soluble in vegetable oils. The melting point of vitamin D<sub>2</sub> lies between 115 and 118 C. Solutions of vitamin D<sub>2</sub> possess an absorption maximum at 2640 angstroms

Dissolve approximately 0.5 mg. of vitamin D<sub>3</sub> in 5 cc. of chloroform, add 3 drops of citric anhydride and 3 drops of sulfuric acid and shake the mixture; a bright red color develops which rapidly changes to violet, blue and finally to green.

Dissolve 0.05 Gm. of vitamin D<sub>3</sub> and 0.65 Gm. of 3,5 dinitrobenzoyl chloride in separate 1 cc. portions of anhydrous pyridine. Mix the solution and warm the mixture on the water bath for ten minutes, add 5 cc. of water, filter and wash the precipitate repeatedly with small amounts of cold water. Recrystallize the precipitated dinitrobenzoyl derivative twice from acetone and finally dry it in a desiccator under partial vacuum; the melting point of the product is from 147 to 149 C.

The specific rotation  $[\alpha]_{\frac{25}{D}}$  of the vitamin D<sub>3</sub> dinitrobenzoate dissolved in acetone + 80 degrees.

Dissolve approximately 0.01 Gm. of vitamin D<sub>3</sub> in 1 cc. of alcohol and add 1 cc. of a 1 per cent solution of d-glutonic in 50 per cent alcohol, allow the mixture to stand for twelve hours; no precipitate occurs (absence of ergosterol).

Dissolve approximately 0.03 Gm. of vitamin D<sub>3</sub>, accurately weighed, in 1 cc. of acetone at 25 C. Polarize the solution in a 0.5 decimeter tube at 25 C. using sodium light; the specific rotation lies between + 79.5 and + 83.5 degrees. Determine the amount of calcium and hydrogen present in vitamin D<sub>3</sub> by burning the substance in an appropriate combustion flask; the carbon content should not be less than 84.6 per cent nor more than 85.1 per cent, the hydrogen content should not be less than 10.9 per cent nor more than 11.3 per cent.

## WINTHROP CHEMICAL COMPANY, INC.

**Drisdol in Propylene Glycol:** 5 cc. and 50 cc. bottles. Each 1 cc. contains 0.25 mg. of drisdol and has a potency of 10,000 units of vitamin D (U. S. P.) per gram. The propylene glycol used in the preparation of this product complies with the standards for propylene glycol-N. S. R.

**Dosage**—Average daily dose: 2 drops dissolved in total ration of modified or whole milk. If administered in water, gruel, etc., 4 drops daily for the average infant, and up to 15 drops daily for the premature or rapidly growing infant. Daily curative dose: 15 to 20 drops. The product is marketed with a special dropper delivering 250 U. S. P. units of vitamin D per drop.

U. S. patents 1,522,765 (March 21, 1932, expires 1950) and 2,012,787 (Feb. 11, 1936, expires 1953) and by license of the Wisconsin Alumni Research Foundation under U. S. patents 1,653,218 (Aug. 14, 1927, expires 1941) and 1,571,376 (Aug. 9, 1932, expires 1948). U. S. trademark 333,601.

## Vitamins A and D Preparations

### FISH LIVER OIL, PREPARATIONS AND CONCENTRATES

The chief fish liver oil used pharmacologically is cod liver oil. Cod liver oil is now widely used as an adjunct in a fattening diet. This oil is rich in both vitamins A and D and is a readily digested fat. By virtue of its vitamin D content, cod liver oil has been demonstrated to have a favorable influence on the metabolism of calcium and phosphorus in general and particularly in the prevention of rickets. In fact it is usual to recommend dosages of cod liver oil for animals and humans in terms of D units or rickets. The U. S. P. defines 1 D unit as 0.000001 g.

8 cc daily, probably provides more than twice as much vitamin A daily as an infant will obtain by breast feeding alone.

The U S Pharmacopeia, besides giving tests for the purity of cod liver oil, also gives methods for the assay of its content of vitamin A and vitamin D, furthermore, it provides that the vitamin A potency and vitamin D potency of cod liver oil when designated shall be expressed in "United States Pharmacopeia units" per gram of oil and may be referred to as "U S P units" per gram of oil. It is also stipulated that

Cod liver oil must contain in each gram at least 850 U S P units of vitamin A and at least 85 U S P units of vitamin D. Cod liver oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in this pharmacopeia.

Obviously, all brands in New and Nonofficial Remedies are required to have a vitamin potency of at least that of the pharmacopeial product.

Statements of the potency of tablet preparations of cod liver oil concentrate made on a 'per tablet' basis and also on a 'per gram of tablet' basis should appear in the firm's presentation and in New and Nonofficial Remedies. On the labels however a declaration of vitamin potency per tablet is sufficient.

At the present time a War Production Board order designed to conserve vitamin A supplies limits the quantity of vitamin A that can be recommended by a manufacturer to be taken daily to not more than 5000 units for many vitamin preparations. The order does not apply to U S P preparations or to "preparations represented to contain 25000 or more U S P Units of vitamin A in the smallest daily dosage recommended by the manufacturer or seller for adult use."

**BLENDED OIL CONTAINING VITAMINS A AND D**—A mixture of fish and/or vegetable oils to which cholesterol may be added. The vitamin A content is not less than 1,800 U S P units per gram and the vitamin D content not less than 175 U S P units per gram.

*Actions and Uses*—See preceding article Vitamins A and D Preparations.

*Dosage*—See preceding article Vitamins A and D Preparations.

Blended oil containing vitamin A and D having a fishy but not rancid odor, slightly soluble in alcohol, benzene, ethyl acetate and carbon tetrachloride. The refractive index is from 1.474 to 1.479 at 25°C.

A solution of one drop of blended oil containing vitamins A and D in 1 cc. of chloroform when shaken with one drop of sulfuric acid acquires a blue color gradually changing to purple. Fill a tall cylindrical tube of about 120 cc capacity with the oil and maintain at 0°C for five hours; the oil remains clear and fluid and deposits no solid material. Dissolve 2 Gm accurately weighed of blended oil containing vitamins A and D in 30 cc of a mixture of equal parts of ether and alcohol.



previously neutralized to phenolphthalein, and boil gently under a reflux condenser for ten minutes. Cool and titrate the mixture with tenth normal sodium hydroxide to the production of a pink color which persists for thirty seconds; not more than 1 cc. of tenth normal sodium hydroxide is required (*free acid*). The unsaponifiable matter in blended oil containing vitamins A and D is not more than 1.5 per cent when determined according to the method as given in the U. S. P. XI. The iodine value is not less than 145 nor more than 180. The saponification value is not less than 186 nor more than 202.

### MEAD JOHNSON & CO., INC.

#### Mead's Blended Oil Containing Vitamins A and D: 1 gallon bottles

U. S. patents 1,680,818 (Aug. 14, 1928, expires 1945) and 1,861,136 (Aug. 9, 1934, expires 1951) under license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under Mead's Vioosterol in Oil, is added to fish liver oil, sardine oil and maize oil, and the finished product is required to have a vitamin A potency of not less than 1,800 units (U. S. P.) per gram and not less than 175 units (U. S. P.) of vitamin D per gram.

**CONCENTRATED OLEOVITAMIN A AND D.**—“Fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of vitamin A and D concentrates in fish liver oil or in an edible vegetable oil. The vitamin A shall be obtained from natural (animal) sources and the vitamin D may be obtained from natural (animal) sources or may be synthetic oleovitamin D. Concentrated Oleovitamin A and D contains in each gram not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A, and not less than 10,000 and not more than 13,000 U. S. P. units of vitamin D.” U. S. P.

For description and standards see the U. S. Pharmacopeia under Oleovitamin A et D Concentrata.

*Actions, Uses and Dosage*.—See under Vitamin A and D preparations (N. N. R., 1943, p. 605).

### WALKER VITAMIN PRODUCTS, INC.

**Concentrated Oleo Vitamin A-D Drops:** Each gram  
 contains 10,000 units of vitamin A and  
 1,000 units of vitamin D. Natural esters  
 of vitamins A and D (in vegetable oils) plus  
 flavored with cinnamon.

**BURBOT LIVER OIL.**—The oil extracted from the livers of the Burbot (*Lota maculosa*), family Gadidae. It is biologically assayed to have a potency of not less than 4,480 units of vitamin A (U. S. P.) per gram and of not less than 640 units of vitamin D (U. S. P.) per gram.

*Actions and Uses.*—Same as those of cod liver oil. See preceding article Vitamins A and D Preparations.

*Dosage*.—Prophylactic, 1 cc (40 drops) daily; or as prescribed by the physician. The product is marketed with a dropper designed to deliver about 25 drops to the cubic centimeter.

*Tests and Standards—*

Burbot liver oil is a pale, yellow, oily liquid. It has a slightly fishy odor. It is slightly soluble in alcohol, benzene, carbon disulfide and ethyl ether.  $n_D^{20}$  0.921 to 0.927 at 25°C. The specific gravity is 0.921 to 0.927 at 25°C. The refractive index is 1.432 at 20°C.

1 cc of chloroform, when shaken with one drop of sulfuric acid, acquires a light violet color, changing to violet, dark green and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for twenty-five minutes at 25°C. no precipitate forms and a clear solution remains.

Fill a tall cylindric standard oil sample bottle of about 120 cc capacity with burbot liver oil at a temperature between 23 and 28°C. stopper, and immerse the bottle in a mixture of ice and distilled water for five hours; the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of burbot liver oil accurately weighed, in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth normal sodium hydroxide, using five drops of phenolphthalein T. S. as indicator, and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds; not more than 1 cc. of tenth normal sodium hydroxide is required (free acid). The amount of unsaponifiable matter as determined by the method of U. S. P. XI page 446, is not less than 0.9 per cent nor more than 3.0 per cent. The saponification value as determined by the method of U. S. P. XI page 445, is not less than 184 nor more than 196. The iodine value as determined by the method of U. S. P. XI page 445, on 0.18 to 0.20 Gm. of sample accurately weighed, is not less than 155 nor more than 180.

**BURBOT LIVER PRODUCTS Co**

**Burbot Liver Oil (Rowell)** 60 cc and 240 cc bottles

**Capsules Burbot Liver Oil (Rowell)** 0.52 cc minimum adjusted to have a potency of not less than 2,215 units of vitamin A (U. S. P.) and 315 units of vitamin D (U. S. P.) per capsule

**COD LIVER OIL**—The partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linne and other species of the family *Gadidae*. *Cod Liver Oil* may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in the U. S. Pharmacopeia. Cod Liver Oil contains in each Gm. at least 850 U. S. P. units of Vitamin A and at least 85 U. S. P. Units of Vitamin D.

The Vitamin A potency and Vitamin D potency of Cod Liver Oil when designated shall be expressed in United States Pharmacopeia Units per gram of oil and may be referred to as 'U. S. P. Units' U. S. P.

For description and standards see the U. S. Pharmacopeia under *Oleum Morrhuae*.

*Actions, Uses and Dosage*—See preceding article *Vitamins A and D Preparations*

**ABBOTT LABORATORIES**

**Cod Liver Oil** 360 cc 480 cc and 384 liter bottles. Each 1 Gm. has a potency of not less than 1,000 U. S. P. units of vitamin A and of not less than 100 U. S. P. units of vitamin D.

**BAY STATE LABORATORIES, INC.**

**Cod Liver Oil:** 120 cc bottles. Each gram contains 2,500 U S P units of vitamin A and 125 U. S P units of vitamin D

**BORCHERDT MALT EXTRACT COMPANY**

**Malt Extract with Cod Liver Oil:** 480 cc bottles. Each 100 cc. contains cod liver oil, 25 cc., and malt extract, 75 cc. Each 1 Gm has a potency of not less than 250 U S P units of vitamin A and of not less than 25 U S P units of vitamin D

**INTERNATIONAL VITAMIN CORPORATION**

**Cod Liver Oil:** 180 cc., 480 cc and 720 cc. bottles. Each 1 Gm. has a potency of not less than 2,000 U S P units of vitamin A and of not less than 200 U S P units of vitamin D

**THE MALTINE COMPANY**

**Maltine with Cod Liver Oil:** 480 cc bottle and 450 Gm and 3.84 liter jars. Each 100 cc. contains cod liver oil, 30 cc., and maltine, 70 cc. Each 1 Gm has a potency of not less than 250 U S. P units of vitamin A and not less than 25 U. S P units of vitamin D

**Maltine with Cod Liver Oil and Iron Iodide:** 480 cc bottle and 450 Gm and 3.84 liter jars. Maltine with cod liver oil to which has been added 0.44 Gm of ferrous iodide per 100 cc. (2 grains to each fluidounce). Each 1 Gm of the preparation has a potency of not less than 500 U S P units of vitamin A and of not less than 50 U S P units of vitamin D

The maltine used in the foregoing products is a preparation essentially similar to extract of malt U S. P., but it contains 19 per cent of alcohol and is prepared from malted barley, oats and wheat

U. S. trademark 44,566.

**MEAD JOHNSON AND COMPANY**

**Cod Liver Oil:** 120 cc., 240 cc and 480 cc bottles. Each 1 Gm has a potency of not less than 1,800 U S. P units of vitamin A and of not less than 175 U. S P units of vitamin D

**Cod Liver Oil Flavored:** 120 cc., 240 cc. and 480 cc bottles. Cod liver oil to which has been added 0.12 per cent of a mixture of U S. P. essential oils as a flavoring agent

**Cod Liver Oil Fortified with Percomorph Liver Oil:** 88 cc., 90 cc. and 480 cc. Consists of Mead's standardized cod liver oil with percomorph and other fish liver oils. Not less than 50 per cent of the vitamin content is derived from percomorph liver oil. Supplies not less than 6,000 U S P units of vitamin A and 850 U. S P. units of vitamin D. Biologically assayed

**PARK, DAVIS & COMPANY**

**Cod Liver Oil** 120 cc 360 cc and 480 cc bottles Each 1 Gm has a potency of not less than 2 000 U S P units of vitamin A and of not less than 250 U S P units of vitamin D

**Soluble Gelatin Capsules Cod Liver Oil** 0.65 cc and 1.3 cc

**Malt Extract with Cod Liver Oil** 480 cc and 3.84 liter bottles Each 100 cc contains cod liver oil, 25 cc, and malt extract (unmedicated), 75 cc with chocolate and vanilla as flavoring

**TITE E. L. PATCH COMPANY**

**Flavored Cod Liver Oil** 120 cc 360 cc and 480 cc bottles Cod liver oil to which has been added 0.5 per cent of essential oils as flavoring Each 1 Gm has a potency of not less than 2 000 U S P units of vitamin A and of not less than 200 U S P units of vitamin D

**E. R. SQUIBB & SONS**

**Cod Liver Oil** 120 cc 360 cc and 720 cc bottles Each 1 Gm has a potency of not less than 1 800 U S P units of vitamin A and not less than 180 U S P units of vitamin D  
U S patent 1 829 571 (Oct 27, 1931, expires 1948)

**Mint-Flavored Cod Liver Oil** 120 cc 360 cc and 720 cc bottles Cod liver oil to which has been added 0.67 per cent of oil of spearmint as flavoring

**TAILBY NASON COMPANY**

**Palatable Cod Liver Oil** 120 cc and 360 cc bottles Cod liver oil containing not over 0.5 per cent of essential oils as flavoring Each 1 Gm has a potency of not less than 1 400 U S P units of vitamin A and of not less than 130 U S P units of vitamin D

**COD LIVER OIL WITH VIOSTEROL**—Viosterol dissolved in cod liver oil, to adjust it to the potency of not less than 850 units (U S P) of vitamin A per Gm 360 units (U S P) of vitamin D per Gm

*Actions and Uses*—See general article Viosterol Cod liver oil with viosterol is proposed for use in conditions in which it is desired to supplement the administration of vitamin A with that of a relatively large amount of vitamin D

*Dosage*—For infants and young children 2.5 to 3.3 cc daily for adults and in severe cases doses up to 7 cc or more are given

*Preparation*—

Cod liver oil with viosterol is prepared by addition of irradiated ergosterol to cod liver oil in such proportion that the finished product will have a potency of not less than 850 units (U S P) of vitamin A per Gm and not less than 360 units (U S P) of vitamin D per Gm

**MEAD JOHNSON AND COMPANY**

**Cod Liver Oil with Viosterol.** 118 cc bottle Each 1 Gm has a potency of not less than 1,800 U S. P. units of vitamin A and of not less than 400 U S. P. units of vitamin D

**PARKE, DAVIS & COMPANY**

**Cod Liver Oil with Viosterol:** 90 cc and 480 cc bottles Each 1 Gm has a potency of not less than 2,000 U S. P. units of vitamin A and of not less than 400 U S. P. units of vitamin D.

**E. R. SQUIBB & SONS**

**Cod Liver Oil with Viosterol:** 90 cc and 480 cc bottles Each 1 Gm has a potency of not less than 2,000 U. S. P. units of vitamin A and of not less than 440 U S. P. units of vitamin D

**Cod Liver Oil with Viosterol, Mint Flavored:** 90 cc and 480 cc. bottles Cod liver oil with viosterol to which has been added 0.67 per cent of oil of spearmint as flavoring

**COD LIVER OIL CONCENTRATE (LIQUID).—**

A concentrate of the nonsaponifiable fraction of cod liver oil dissolved in cod liver oil or in neutral vegetable oil. Preparations of cod liver oil concentrate having a vitamin A potency of not less than 50,000 and not more than 65,000 units per gram and a vitamin D potency of not less than 5,000 and not more than 6,500 units per gram will be considered for acceptance

*Actions and Uses*—Cod liver oil concentrate (liquid) possesses properties similar to those of cod liver oil so far as these depend on the vitamin content of the latter.

*Dosage*—Prophylactic For liquids 6 to 12 drops daily For capsules 1 or 2 capsules daily

Cod liver oil concentrate is made under U S patent 1,690,091 (October 30, 1928; expires 1945) or under U S patent 1,984,858 (December 18, 1934; expires 1951)

**CLINADOL CO., INC.**

**Cod Liver Oil Concentrate:** 60 cc bottles, packaged with a dropper designed to deliver approximately 1 minim per drop An extract of the nonsaponifiable fraction of cod liver oil in maize oil, to which has been added saccharin (3 in 10,000) and oil of cassia, 2 per cent Each 1 Gm. of the concentrate has a potency of not less than 60,000 U S. P. units of vitamin A and of not less than 6,000 U S. P. units of vitamin D

U. S. trademark 279,325.

**INTERNATIONAL VITAMIN CORPORATION**

**Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil:** bulk. Each 1 Gm has a potency of not less than 60,000 U. S. P. units of vitamin A and of not less than 8,500 U. S. P. units of vitamin D.

**Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil** 6 cc and 60 cc bottles Each packaged with a dropper designed to supply 48 drops per gram Each drop has a potency of not less than 1250 U S P units of vitamin A and not less than 175 U S P units of vitamin D

**Capsules Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil** 0.195 cc Each capsule has a potency of not less than 5000 U S P units of vitamin A and not less than 1000 U S P units of vitamin D

#### **McKesson & Robbins, Inc**

**Natural Vitamins A and D in Oil** 6 cc vials A concentrate of vitamins A and D prepared from cod liver oil the concentrate containing not less than 60,000 U S P units of vitamin A and not less than 10,000 U S P units of vitamin D per gram

#### **S M A CORPORATION**

**Carotene with Vitamin D Concentrate in Oil** (See under Carotene)

#### **WHITE LABORATORIES, INC**

**Cod Liver Oil Concentrate Liquid** bulk A cod liver oil concentrate dissolved in cod liver oil having a potency of not less than 55,000 U S P units of vitamin A and of not less than 5,500 U S P units of vitamin D per gram

**Cod Liver Oil Concentrate Capsules** 0.195 cc Each capsule has a potency of not less than 5,000 U S P units of vitamin A and of not less than 500 U S P units of vitamin D

**Cod Liver Oil Concentrate Liquid** 6 cc 30 cc and 60 cc vials packaged with a dropper designed to supply in each 2 drops (0.062 cc) a potency of not less than 3,120 U S P units of vitamin A and of not less than 312 U S P units of vitamin D

**COD LIVER OIL CONCENTRATE TABLETS**—Cod liver oil in the form of tablets having a potency of not less than 3,120 U S P units of vitamin A and of not less than 312 U S P units of vitamin D

*Actions and Uses*—Cod Liver Oil Concentrate Tablets possess properties similar to cod liver oil so far as these depend on the fat soluble vitamin content of the latter

*Dosage*—Two to six tablets daily

#### **INTERNATIONAL VITAMIN CORPORATION**

**Tablets Concentrate of Vitamins A and D from Cod Liver Oil** Each tablet has a potency of not less than 3,150 U S P units of vitamin A and of not less than 315 U S P units of vitamin D

## WHITE LABORATORIES, INC.

**Tablets Cod Liver Oil Concentrate:** Each tablet has a potency of not less than 3,150 U. S. P. units of vitamin A and of not less than 315 U. S. P. units of vitamin D.

**HALIBUT LIVER OIL.**—"The fixed oil obtained from the fresh, or suitably preserved livers of *Hippoglossus hippoglossus* Linne (Fam. *Pleuronectidae*). Halibut Liver Oil contains in each Gm. not less than 60,000 U. S. P. units of vitamin A and not less than 600 U. S. P. units of vitamin D.

The vitamin A potency and vitamin D potency of Halibut Liver Oil, when designated on the label, shall be expressed in 'United States Pharmacopeia Units' per Gm. of oil and may be referred to as 'U. S. P. Units.'

Halibut Liver Oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in this Pharmacopeia." U. S. P.

For description and standards see the U. S. Pharmacopeia under *Oleum Hippoglossi* and *Capsulae Olei Hippoglossi*.

**Actions and Uses.**—Halibut Liver Oil is used mainly as a source of vitamin A. See general article on Vitamin A.

**Dosage.**—For infants, 6 to 10 drops (25 to 35 minims) daily; for premature and rapidly growing infants, 15 drops (525 minims daily. For severe vitamin deficiencies, 20 drops (7 minims) or more may be given at the discretion of the physician. The accepted preparations are marketed with an accompanying dropper designed to deliver a certain number of drops to the minim.

## ABBOTT LABORATORIES

**Haliver Oil, Plain:** 10 cc. and 50 cc. bottles. Each 1 Gm. has a potency of not less than 60,000 U. S. P. units of vitamin A and of approximately 1,000 U. S. P. units of vitamin D.

**Haliver Oil Plain Capsules:** 0.695 cc. Each capsule has a potency of not less than 5,000 U. S. P. units of vitamin A.

U. S. patent No. 2,116,031 (Dec. 19, 1937, expires 1953). "Haliver" is registered as a trademark No. 294,822.

## INTERNATIONAL VITAMIN CORPORATION

**Halibut Liver Oil, Plain:** 11 cc. and 61 cc. bottles. Each 1 Gm. has a potency of not less than 50,000 U. S. P. units of vitamin A and of approximately 1,000 U. S. P. units of vitamin D.

**Capsules Halibut Liver Oil, Plain:** 0.15 cc. Each capsule has a potency of not less than 1,000 U. S. P. units of vitamin A and of not less than 120 U. S. P. units of vitamin D.

**MCKESSON & ROBBINS, INC**

**Halibut Liver Oil Plain** 11 cc vials Each 1 Gm has a potency of not less than 60 000 U S P units of vitamin A and of approximately 1 000 U S P units of vitamin D

**Capsules Halibut Liver Oil Plain** 0 098 cc Each capsule has a potency of not less than 5 000 U S P units of vitamin A and of not less than 85 U S P units of vitamin D

**MILB JOHNSON AND COMPANY**

**Halibut Liver Oil** 10 cc and 50 cc bottles Each 1 Gm has a potency of not less than 60 000 U S P units of vitamin A and of approximately 850 U S P units of vitamin D

**PAHKE, DAVIS & COMPANY**

**Haliver Oil, Plain** 10 cc and 50 cc bottles Each 1 Gm has a potency of not less than 60 000 U S P units of vitamin A and of approximately 1 000 U S P units of vitamin D

**Soluble Gelatine Capsules Haliver Oil Plain** 0 195 cc Each capsule contains haliver oil plain 3 minims with sufficient cod liver oil to fill the capsule

No U S patent Halver is registered as trademark no. 294 69

**L R SQUINN & SONS**

**Halibut Liver Oil Plain** 10 cc vial and 50 cc bottle Each 1 Gm has a potency of not less than 60 000 U S P units of vitamin A and 1 000 U S P units of vitamin D

**Soluble Gelatine Capsules Halibut Liver Oil Plain** 0 098 cc Each capsule contains approximately 5 drops or 1 cc halibut liver oil plain which supplies 5 000 U S P units of vitamin A and 85 U S P units of vitamin D

**FREDRICK STEARNS & COMPANY**

**Capsules Halibut Liver Oil Plain** 0 195 cc Each capsule has a potency of not less than 10 000 U S P units of vitamin A and of not less than 170 U S P units of vitamin D

**THE UPJOHN COMPANY**

**Capsules Halibut Liver Oil** 0 2 cc Each capsule has a potency of not less than 10 000 U S P units of vitamin A and not less than 170 U S P units of vitamin D

**COD AND HALIBUT LIVER OIL**—A blend of cod and halibut liver oils adjusted to a potency of not less than 3 600 nor more than 5 000 U S P units of vitamin A per gram and of not less than 360 nor more than 500 U S P units of vitamin D per gram.

*Actions and Uses*—Cod and Halibut Liver Oil is used mainly as a source of vitamin A

*Dosage*—2 cc supplies the average prophylactic dose of natural vitamins A and D



**HALIBUT LIVER OIL WITH VIOSTEROL.**—Halibut liver oil to which has been added sufficient viosterol (activated ergosterol) to assure a potency of not less than 10,000 U. S. P. units of vitamin D per gram.

*Actions and Uses*—The same as those for cod liver oil (See general article, Vitamins A and D preparations)

*Dosage*—For infants, 8 to 10 drops (about 0.6 cc.) daily; for premature and rapidly growing infants, 15 drops (about 0.3 cc.) daily; for older children, 15 to 20 drops (0.3 to 0.42 cc.) daily; for adults, especially nursing and expectant mothers, 20 drops (about 0.42 cc.) or more daily. The marketed preparation is accompanied by a special dropper designed to deliver a certain number of drops to the minimum.

#### ABBOTT LABORATORIES

**Haliver Oil with Viosterol.** 5 cc., 20 cc. and 50 cc. bottles.

**Soluble Gelatin Capsules Haliver Oil with Viosterol.** 0.09 cc. Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,000 U. S. P. units of vitamin D.

#### INTERNATIONAL VITAMIN CORPORATION

**Halibut Liver Oil with Viosterol in Oil.** 6 cc., 10 cc. and 60 cc. bottles.

**Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil:** 0.195 cc. Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

#### MCKENNON & ROBBINS, INC.

**Halibut Liver Oil with Viosterol in Oil:** 6 cc. and 60 cc. bottles.

**Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil:** 0.195 cc. Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

#### MILES JOHNSON AND COMPANY

**Viosterol in Halibut Liver Oil:** 10 cc. and 60 cc. bottles.

**Capsules Viosterol in Halibut Liver Oil:** 0.195 cc. Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

#### PARK, DAVIS & COMPANY

**Haliver Oil with Viosterol:** 5 cc., 20 cc. and 50 cc. bottles.

**Soluble Gelatin Capsules Haliver Oil with Viosterol:** Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

**E. R. SQUIBB & SONS**

**Soluble Gelatine Capsules Halibut Liver Oil with Viosterol**· 0.098 cc Each capsule supplies 5,000 U S P units of vitamin A and 1000 U S P units of vitamin D

**PERCOMORPH LIVER OIL** — *Oleum Percomorphum*  
 fresh  
 Pneur  
 —som

*Sarda chiliensis*, *Germo alalunga*, *Thunnus orientalis*, *Scomber scombrus*, *Seriola dorsalis*, *Lutianus campechanus*, *Epinephelus morio*, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishimagi* and *Sphyraena argentea*, containing not more than 50 per cent of other fish liver oil. It is biologically assayed to have a potency of not less than 60,000 units of vitamin A (U S P) per gram and of not less than 8,500 units of vitamin D (U S P) per gram.

**Actions and Uses** — Same as those of cod liver oil. See general article, *Vitamins A and D Preparations*.

**Dosage** — Prophylactic, for normal infants, 10 drops daily, curative, and in severe conditions, to 20 drops daily. The product is marketed with a dropper designed to deliver 44 drops to the cc.

**Tests and Standards** —

Percomorph liver oil, 50% in fish liver oil is a yellow to brownish yellow oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.922 to 0.930 at 25 C. The refractive index is from 1.480 to 1.485 at 20 C.

A solution of one drop of the oil in 1 cc of chloroform, when shaken with one drop of sulfuric acid, acquires a blue color, changing to violet, dark green, and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for twenty five minutes at 25 C.; no precipitate forms and a clear solution remains.

Fill a tall, cylindrical, standard oil sample bottle of about 120 cc capacity with percomorph liver oil, 50%, in fish liver oil, at a temperature between 23 and 28 C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours. The oil remains fluid and forms no deposit.

oil 50%, in fish liver oil in alcohol and ether which precipitates normal sodium hydroxide, using indicator, and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds not more than 1 cc of tenth normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of U S P is not less than 3.5 per cent nor more than 7 per cent, it is semisolid in appearance. The saponification value as determined by the method of U S P is not less than 174 and not more than 186. The iodine value as determined by the method of U S P on 0.18 to 0.20 Gm of sample, accurately weighed is not less than 145 and not more than 180.

The undiluted fixed oil obtained from the fresh livers of the percomorph fishes and used in the preparation of percomorph liver oil 50 per cent in fish liver oil conforms to the following constants as determined by methods of U S P: specific gravity from 0.924 to

0.930 at 25 C; refractive index, from 1.484 to 1.490 at 20 C, free acid in 2 Gm, equivalent to not more than 1 cc of tenth normal sodium hydroxide, unsaponifiable matter, not less than 7 nor more than 13 per cent (semi-solid in appearance); saponification value, not less than 168 nor more than 182, iodine value, not less than 145 nor more than 180

FLINT, EATON & COMPANY

**Ofeum Percomorphum:** 8 cc bottle

## MEAD JOHNSON AND COMPANY

**Oleum Percomorphum with Other Fish-Liver Oils and Viosterol:** A blend of liver oils of percomorph fishes, viosterol and other fish liver oils. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the livers of percomorph fishes. Each gram contains not less than 60,000 U. S. P. units of vitamin A and 8,500 U. S. P. units of vitamin D.

**Oleum Percomorphum with Other Fish-Liver Oils and  
Vioosterol: 50 cc bottles**

**Capsules Oleum Percomorphum with Other Fish-Liver Oils and Viosterol:** Each capsule contains 85 mg of oleum percomorphum with other fish liver oils and viosterol and supplies a potency of 5,000 U S P units of vitamin A and 700 U. S. P. units of vitamin D.

**SHARK LIVER OIL.**—The oil extracted from the livers of the shark, mainly of the variety *Hypoprion brevirostris* (lemon), but any or all of the following varieties may be included. *Odontaspis littocaris* (sand), *Isurus punctatus* (mackerel), *Triakis semifasciatus* (leopard), *Sphyrna zygaena* (hammerhead), *S. tiburo* (nurse), *S. tiburo* (black t), *S. tiburo* (black t) of not less than and of not less than the latter is insu.

**Actions and Uses**—See the general article, Vitamins A and D

**Preparations**

**Dosage.**—One capsule, or about 0.52 cc., daily

### Tests and Standards—

Chickadee

the bath is warmed to 45°C

**LIST OF ARTICLES AND BRANDS  
ACCEPTED BY THE COUNCIL  
BUT NOT DESCRIBED  
IN N. N. R**

*Medicinal Articles*—Articles which have been examined by the Council, which are marketed under descriptive, nonproprietary names with well established therapeutic claims, and which are held by the Council not to require description in New and Nonofficial Remedies

**CUTTER LABORATORIES**

Diphtheria Antitoxin Concentrated  
Smallpox Vaccine  
Tetanus Antitoxin Concentrated

**THE GILLILAND' LABORATORIES, INC**  
Concentrated and Refined Diphtheria Antitoxin  
Concentrated and Refined Tetanus Antitoxin  
Smallpox Vaccine

**LEDERLE LABORATORIES, INC**  
Glycerinated Allergenic Extracts  
Smallpox Vaccine (Vaccine Virus)  
Smallpox Vaccine (Preserved with Brilliant Green)

**ELI LILLY AND COMPANY**  
Diphtheria Antitoxin (Purified, Concentrated)  
Tetanus Antitoxin  
Smallpox Vaccine

**THE NATIONAL DRUG CO**  
Diphtheria Antitoxin  
Smallpox Vaccine (Vaccine Virus)  
Tetanus Antitoxin

**NEW YORK CITY DEPARTMENT OF HEALTH**  
Tetanus Antitoxin  
Diphtheria Antitoxin (Globulin)

**PARKE DAVIS & COMPANY**  
Diphtheria Antitoxin, Refined and Concentrated  
Smallpox Vaccine  
Tetanus Antitoxin, Refined and Concentrated

## SHARP &amp; DOHME, INC.

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Smallpox Vaccine

Tetanus Antitoxin

Theobromine with Sodium Salicylate

## E. R. SQUIBB &amp; SONS

Diphtheria Antitoxin

Smallpox Vaccine

Tetanus Antitoxin, Purified

## U. S. STANDARD PRODUCTS CO.

Diphtheria Antitoxin Refined and Concentrated

Smallpox Vaccine (Vaccine Virus)

Tetanus Antitoxin

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*Nonmedicinal Articles*—Articles which have been examined by the Council, which are not advertised as therapeutic agents, the composition or essential ingredients of which are quantitatively declared on the label or in the advertising, and the use of which under ordinary circumstances is, in the opinion of the Council, not contrary to the public welfare

## MERAX, INC.

Merax Mercury Cyanide Solution



## BIBLIOGRAPHIC INDEX TO MEDICINAL ARTICLES NOT INCLUDED IN N.N.R.

This cumulative index is intended to aid the reader in determining the status of articles which do not stand accepted by the Council and to supply him with sources of useful information on such articles. It provides a ready reference to reports of the Council on Pharmacy and Chemistry explaining the rejection of an article or the omission from New and Non-official Remedies of a previously accepted preparation, to reports of the A. M. A. Chemical Laboratory on unacceptable products, and to critical editorial comments and brief notes in *The Journal of the American Medical Association* pertaining to therapeutic agents not accepted for N.N.R. References to preliminary reports of the Council, which as a rule deal with new articles possessing potential acceptability for N.N.R., are not included.

For an article or subject  
may be obtained by  
the Council

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M. A., if it appeared

there; and, second, for the benefit of those that do not have access to files of *The Journal*, the place where a discussion of the article may be found in other publications: "Reports of the Council on Pharmacy and Chemistry," "Propaganda for Reform" and "Reports of the A. M. A. Chemical Laboratory." Council reports include reports on articles that have been considered by the Council, either at the request of the manufacturers or on the Council's own initiative. The names of the manufacturers (or their agents) follow the names of the preparations, except in those instances in which a drug is discussed in general, without reference to the product of any particular manufacturer.

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## (Fluor) (Winthrop)

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## Sodium (Powder) (Winthrop)

## Sodium (Powder) Ampuls (Winthrop)

## Sodium in Propylene Ampuls Solution (Winthrop)

## Sodium Tablets (Winthrop)

## Tablets (Winthrop)

## I nosol (Liquid)

## Liquid (Hille)

## Unguentum (Hille)

## Magma of Bismuth

## Magnesium Phosphate Trisilicate

## Phosphate Tribasic (Powder) (Merck)

## Trisilicate

## Trisilicate (Powder) (Mallinckrodt)

## Trisilicate Tablets (Burroughs Wellcome)

## Trisilicate Tablets (Lakeside)

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## Extract with Cod Liver Oil (H. D. &amp; Co.)

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## with Cod Liver Oil and Iron Iodide (Maltine)

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## Acid (Powder) (Calco)

## Acid (Powder) (Gane &amp; Ingram)

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# ERRATUM

For the formula of ~~Apocynine Hydrochloride~~  
 substitute the following:

